NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Bristol-Myers Squibb
   a. **Company summary of information for patients (SIP)**

2. **Clarification questions and company responses**
   a. **Results addendum**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Melanoma Focus

4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRiG)

5. **External Assessment Report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Heather Shaw, Consultant Medical Oncologist – clinical expert, nominated by BMS
   b. Mark Harries, Consultant in Medical Oncology – clinical expert, nominated by Melanoma Focus *(*see item 3a)*
   c. Jonathan Haines – patient expert, nominated by Melanoma Focus

8. **Technical engagement responses from stakeholders:**
   a. MSD

9. **External Assessment Report critique of company response to technical engagement** prepared by LRiG
   a. Updated cure proportions

10. **EAG response to NICE requests following ACM1**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Document B

Company evidence submission

April 2023

File name	Version	Contains confidential information	Date
ID1688_Opdualag_STA_Document B_28042023_[ACIC]	**V2.0**	**Yes**	**28th April 2023**

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BICR	Blinded independent central review
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen
DMC	Data monitoring committee
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eMIT	Drugs and pharmaceutical electronic market information tool
FDC	Fixed dose combination
HCRU	Healthcare resource use
HR	Hazard ratio
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMAE	Immune-mediated adverse event
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
LAG-3	Lymphocyte-activation gene-3
LDH	Lactate dehydrogenase
LS	Least-squares
MID	Minimally important difference
NCI	National Cancer Institute
NMA	Network meta-analysis
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PD	Progressed disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1

Abbreviation	Definition
PFS	Progression-free survival
PR	Partial response
PSSRU	Personal Social Services Research Unit
Q4W	Every 4 weeks
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TA	Technology appraisal
TRAE	Treatment-related adverse event
TRSAE	Treatment-related serious adverse event
TTD	Time to Treatment Discontinuation
ULN	Upper limit of normal range
UV	Ultra-violet
WHO	World Health Organization

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's anticipated full marketing authorisation for this indication:

[redacted]

The decision problem addressed in this submission is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 12 years and older with previously untreated unresectable or metastatic melanoma	As per final scope	N/A
Intervention	Nivolumab-relatlimab	As per final scope	N/A
Comparator(s)	• Nivolumab • Nivolumab with ipilimumab • Pembrolizumab	As per final scope	N/A
Outcomes	The outcome measures to be considered include: • Progression-free survival • Overall survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per final scope	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken	No PD-L1 testing in included in the economic analysis.	PD-L1 testing is not considered for treatment decision making in untreated unresectable or metastatic melanoma.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	into account. The economic modelling should include the costs associated with diagnostic testing for PD-L1 expression in people with melanoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See Section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introductionto-health-technology-evaluation).		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • PD-L1 expression (≥ 1% or < 1%) • *BRAF* V600 mutation status	Pre-planned subgroup analyses that include PD-L1 and *BRAF* subgroups are presented in the clinical section only; these subgroups are not considered relevant for cost-effectiveness analyses.	The current management pathway does not consider PD-L1 or *BRAF* status for first-line treatment decisions. This will not change with the introduction of nivolumab-relatlimab.
Key: N/A, not applicable; NHS, National Health Service; PSS, Personal and Social Services; PD-L1, programmed cell death ligand-1; QALY, quality-adjusted life year.			

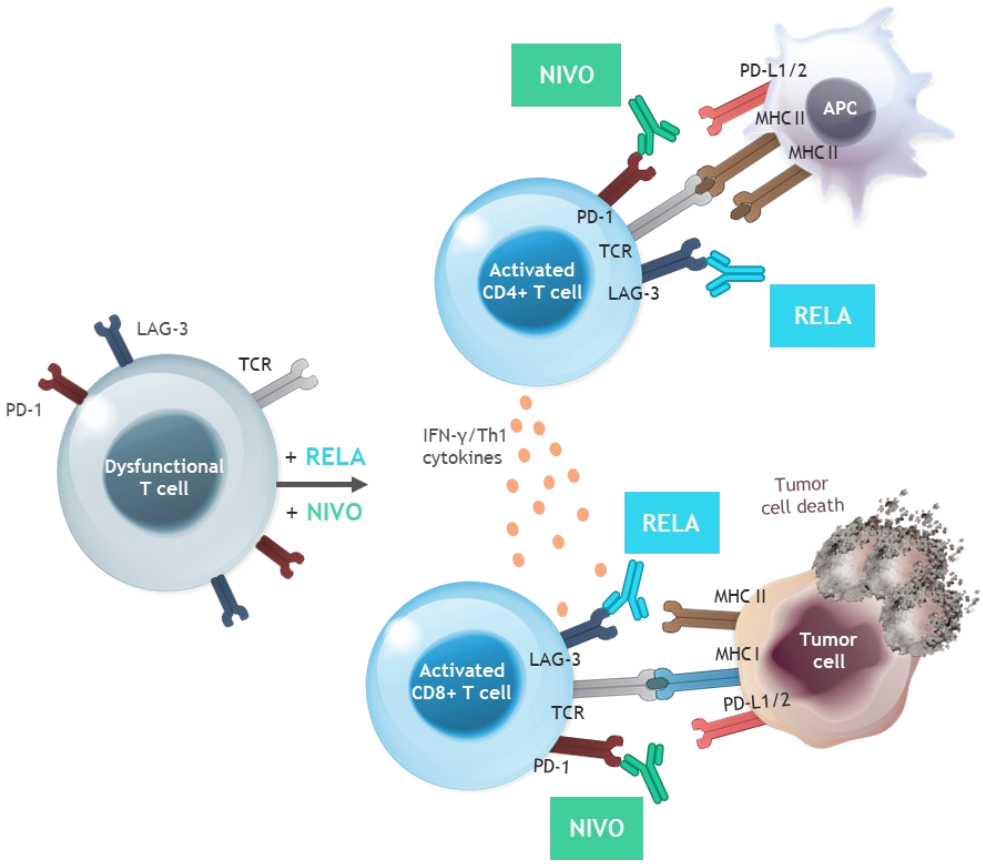
B.1.2. Description of the technology being evaluated

Immunotherapy with checkpoint inhibitors, such as programmed cell death-ligand 1 (PD-L1) inhibitors, has transformed the treatment landscape for patients with advanced melanoma, both as monotherapies and in combination with complementary checkpoint inhibitors.

Nivolumab-relatlimab (Opdualag®, BMS) is the first dual immuno-oncology (IO) fixed-dose combination (FDC) to demonstrate that targeting both lymphocyte-activation gene-3 (LAG-3) and programmed cell death-1 (PD-1) can be an effective approach for treating patients with advanced melanoma. Nivolumab is a proven standard-of-care PD-1 immune checkpoint inhibitor, and is already used to treat melanoma and various other cancer types.[1] Relatlimab is the first FDA-approved drug to block the activity of LAG-3, a cell surface molecule that is expressed on immune cells and negatively regulates T-cell proliferation and effector T-cell function. LAG-3 is known to be upregulated in many tumour types, including melanoma.[2-4] Figure 1 presents the mode of action for nivolumab-relatlimab.

Nivolumab blocks the PD-1 receptor expressed by activated T-cells and B-cells, thereby preventing binding of the PD-1 receptor with its ligands, PD-L1 and PD-L2. This results in a downregulation of the immune response. Inhibition of the interaction between PD-1 and its ligands by nivolumab promotes tumour antigen-specific T-cell responses.[5] Relatlimab is a first-in-class human immunoglobulin G4 LAG-3-blocking monoclonal antibody that binds to LAG-3 and acts to restore the effector function of dysfunctional T-cells while promoting cytokine secretion. In combination with nivolumab, relatlimab works to modulate immune checkpoint pathways that have the capacity to enhance anti-tumour immune responses.[6, 7]

Figure 1: Mechanism of action for nivolumab-relatlimab



Key: APC, antigen-presenting cell; LAG-3, lymphocyte-activation gene-3; MHC, major histocompatibility complex; NIVO, nivolumab; PD-1, programmed cell death-1; PD-L1/2, programmed cell death-ligand 1/2; RELA, relatlimab; TCR, T-cell receptor.
Source: Internal BMS material (Data on file)

Table 2 presents the description of nivolumab-relatlimab. The Summary of Product Characteristics (SmPC) is presented in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Nivolumab-relatlimab (Opdualag®)
Mechanism of action	Nivolumab-relatlimab is an FDC of nivolumab, an anti-PD-1 inhibitor, and relatlimab, an anti-LAG-3 inhibitor. Please refer to Figure 1 and accompanying text for further information.
Marketing authorisation/CE mark status	The application for marketing authorisation with the MHRA is currently ongoing. Approval is expected in [redacted].

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication under appraisal is: [redacted][8]
Method of administration and dosage	The recommended dose for adults and adolescents ≥ 12 years of age is 480 mg nivolumab + 160 mg relatlimab every 4 weeks administered as an IV over 30 minutes.[8] This dose is established for adolescent patients weighing at least 30 kg. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability.[8]
Additional tests or investigations	No additional tests are required.
List price and average cost of a course of treatment	The list price for nivolumab-relatlimab is £[redacted] per vial.
Patient access scheme (if applicable)	A simple discount of [redacted] will be applied
Key: FDC, fixed dose combination; IV, intravenous; lymphocyte-activation gene-3; PD-1, programmed cell death-1.	

B.1.3. Health condition and position of the technology in the treatment pathway

Summary of key points:

- Melanoma is one of the most aggressive and fatal forms of malignancy, and is responsible for approximately 90% of all skin-cancer-related deaths[9, 10]
- The incidence of melanoma is expected to increase by around 9% between 2023–2025 and 2038–2040[11]
- HRQL declines substantially over time with disease progression, with patients declining in almost all major functional areas[12]
- Melanoma has the highest loss of economic productivity cost in Europe compared with other cancers[13]
- The prognosis for patients with untreated unresectable or metastatic melanoma is poor. In patients diagnosed between 2013 and 2017, the 5-year survival rate for patients with Stage III melanoma was 70.6%, and non-estimable (NE) for patients with Stage IV melanoma[14]

- The introduction of immuno-oncology (IO) therapies to the melanoma treatment landscape has increased the 5-year overall survival (OS) rate. Data from the CheckMate-067 trial demonstrated a 5-year OS rate of 52% in patients receiving nivolumab + ipilimumab and 44% in patients receiving nivolumab monotherapy[15]
- Existing dual IO treatment demonstrates improved outcomes compared with single-agent programmed cell death-1 (PD-1) inhibitors, but also increased toxicity. Hence, there is need for a dual IO treatment with a safety profile that is generally manageable with standard protocols
- An additional dual IO treatment, with an optimised risk–benefit profile, would allow a greater proportion of patients with advanced melanoma to benefit from more efficacious treatment

B.1.3.1. Disease background

Melanoma is a tumour produced by the malignant transformation of melanocytes, highly differentiated skin cells that produce the protective skin-darkening pigment melanin.[16] Although melanoma is less common than other skin cancers, representing approximately 1% of all skin cancers, it is one of the most aggressive and fatal forms of malignancy and accounts for 90% of all skin-cancer-related deaths.[9]

Melanoma most commonly arises in cutaneous primary locations but can also arise within the mucosal surfaces of the body (mucosal melanoma), the uvea of the eye (uveal melanoma), or cutaneous locations in non-hair-bearing surfaces (acral melanoma), including palms of hands, soles of feet.[17] In some cases, melanoma is diagnosed as metastatic without a known primary site, which is called unknown primary melanoma.[17]

Though a handful of mutations involved in melanoma development may be inherited, the majority of melanomas arise from somatic mutations acquired later in life.[9] Approximately 50% of all melanomas contain activating *BRAF* mutations, a serine/threonine protein kinase that activates the MAPK/ERK signalling pathway.[18] The most common of the *BRAF* mutations is V600E, which equates to > 85% of *BRAF* mutations, and are most common in females, younger patients and in patients

whose tumours arise on skin without chronic sun-induced damage.[9, 18, 19] Of note, IO therapies have demonstrated efficacious outcomes irrespective of a patient's *BRAF* mutation status. Other common genomic subtypes include mutant *NRAS* and mutant *NF1*, which can be identified in approximately 15–20% and 10–15% of melanomas, respectively.[18]

Ultra-violet (UV) light exposure remains the most widely recognised environmental risk factor for melanoma from different sources such as sun and tanning beds.[20, 21] This is due to the association between cumulative UV light exposure and a high number of somatic mutations in the melanoma genome.[22] People are also at an increased risk of melanoma development if they have fair skin, red or blonde hair, a predisposition to the condition and/or the presence of atypical or numerous moles (e.g. > 100 moles).[23]

There are a number of prognosis factors in melanoma, including the age of the patient, speed of diagnosis, staging and location of metastasis, lactate dehydrogenase (LDH) levels, and Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis and age.[24-26] Stage IV (metastatic) disease and poor performance status at diagnosis have the poorest prognosis.[25, 27]

The most commonly used staging system in melanoma is the American Joint Committee on Cancer (AJCC; 8th edition), as summarised in Appendix M.[28] This submission focuses on treatment for patients with untreated unresectable or metastatic cancer which, when using the AJCC cancer staging system, is classified as Stage III or Stage IV melanoma.

B.1.3.2. Clinical and humanistic burden of disease

The characteristic signs of early melanoma are recognised with the well-known ABCDE mnemonic, as presented in Table 3. The first visible sign of a melanoma is often a new mole, or a change in appearance of an existing mole.[29]

Table 3: The ABCDE checklist

A	Asymmetry
B	Border: irregular, ragged, notched, or blurred edges
C	Colour: non-uniform

D	Diameter: larger than 6 mm
E	Evolving: changing in size, shape or colour
Source: Sundarajan et al. 2021[29]	

Initially, melanoma is normally asymptomatic and, if detected early and is localised, can be treated successfully with surgical resection in the majority of cases.[19] However, some individuals present with, or subsequently develop, metastatic melanoma, which can lead to more severe symptoms such as pain, fatigue, weight loss, loss of appetite, nausea and shortness of breath.[30] The prognosis for patients with distant metastases from melanoma is poor, and historically, the vast majority of those with Stage IV melanoma would die from their disease (Section B.1.3.3, Table 4).

Alongside physical symptoms, melanoma impacts psychological functioning. Approximately one-third of patients with melanoma experience considerable levels of distress, mostly at the time of diagnosis and following treatment, and the impact of melanoma on patients' health-related quality of life (HRQL) is comparable to that of other cancers.[31] In patients with metastatic melanoma, a systematic literature review (SLR) examining the effect of treatment on HRQL concluded that patients were found to have a high level of functioning at initial diagnosis; however, as the disease progresses, patients begin to decline in almost all of the major functional areas assessed by the HRQL scales, aligning with an increase in symptoms of their disease and the adverse effects of the therapies used to treat the illness.[12] Since this review was conducted, new immunotherapy treatment options (e.g. nivolumab + ipilimumab, nivolumab monotherapy) have been introduced to the treatment landscape. These treatments have been shown to maintain the quality of life of patients from diagnosis and throughout the trial period.[32]

Unresectable or metastatic melanoma also places a significant financial burden on patients and society. In fact, melanoma has the highest loss of economic productivity cost in Europe (estimated at €312,798/death in 2008) compared with other cancers.[13] This was due to the relatively young age distribution of patients with melanoma and the fact that significant proportions of deaths occur in age groups where wages are highest.

B.1.3.3. Epidemiology

Melanoma is the fifth most common cancer in the UK, accounting for 4% of all new cancer cases.[33] Based on data from 2016–2018, the average number of new melanoma cases in England per year is 14,139.[11]

The incidence of melanoma in the UK has been growing. Over the last decade, the incidence rates of melanoma have increased by around one-third (32%) and are expected to rise by 9% between 2023–2025 and 2038–2040.[11]

Between 2013 and 2017, 62,656 cases of melanoma were diagnosed in adults (aged 15–99) in England, of which 5,199 (8.3%) were Stage III or IV.[14] This equates to approximately 1,040 Stage III or IV melanoma cases diagnosed in England each year. The stage of melanoma was unknown/missing for 5,216 (~8%) melanoma cases. The lack of staging information may in some cases reflect advanced stage at diagnosis as very unwell patients may not undergo staging tests if the invasiveness of the testing outweighs the potential benefit of obtaining stage information. The proportion of patients with late-stage melanoma is therefore likely an underestimation.[34]

Survival rates for patients with melanoma with late-stage disease are relatively poor. Table 4 presents the 1-year and 5-year survival rates in England for adults diagnosed with melanoma between 2013 and 2017. Whilst 100% of patients diagnosed with Stage I melanoma survive for at least a year, only 53% of Stage IV patients survive up to 1 year.[34] In recent years, a number of new immuno-oncology (IO) treatments have been approved for the treatment of advanced melanoma (i.e. nivolumab + ipilimumab, nivolumab monotherapy and pembrolizumab monotherapy). Since their approval, the current survival rates for advanced melanoma are expected to have improved. For example, in the CheckMate-067 trial, patients with advanced melanoma treated with nivolumab + ipilimumab demonstrated a 7.5-year survival rate of 48%.[35] These improved survival rates with nivolumab + ipilimumab are however associated with higher toxicity.

Table 4: Age standardised 1-year and 5-year net survival for adults (15–99 years) diagnosed between 2013 and 2017 in England

Stage	Number of patients	1-year net survival (%)	5-year net survival (%)
Stage I	40,058	100.0	99.6
Stage II	12,174	98.2	80.4
Stage III	3,752	94.7	70.6
Stage IV	1,447	53.0	NE

Key: NE, non-estimable.
Source: Office of National Statistics, 2019[14]

B.1.3.4. Clinical care pathway and proposed positioning of the technology

B.1.3.4.1. Current clinical guidelines and relevant comparators for nivolumab-relatlimab

The prompt diagnosis of melanoma constitutes the cornerstone of an optimal management plan. Early-stage melanoma can be often cured by surgery alone (i.e. resection), and survival rates are high; once the disease has progressed and/or metastasised, survival rates drop significantly (Table 4).[19]

The most recent guidelines for the treatment of untreated unresectable or metastatic melanoma in UK clinical practice are the NICE melanoma assessment and management guidelines (NG14, 2022).[36] These guidelines recommend the first-line treatment of immunotherapy and that clinicians consider the following factors when deciding on a patient's most appropriate treatment:

- Comorbidities and performance status
- Risk of treatment toxicity
- Whether potential treatment toxicity will be tolerated
- Presence of symptomatic brain metastases
- Tumour biology (e.g. high disease burden, rapid progression, LDH level)

The NICE guidelines recommend nivolumab + ipilimumab as the primary choice immunotherapy treatment. When treatment with nivolumab + ipilimumab is

unsuitable or unacceptable (i.e. due to potential toxicity), pembrolizumab or nivolumab monotherapy should be offered.

While the NICE guidelines recommend nivolumab + ipilimumab as the primary choice immunotherapy treatment, UK clinicians have expressed the opinion that the choice of treatment is individualised and ultimately based on its suitability for the patient.[37]

Only when first-line treatment with immunotherapy is contraindicated or unsuitable are alternative, non-immunotherapy treatments considered (e.g. BRAF/MEK inhibitors such as encorafenib + binimetinib or dabrafenib + trametinib).[36] As BRAF/MEK inhibitors are only recommended in patients who are unsuitable for immunotherapy, they are not considered to be relevant comparators to the immunotherapy of nivolumab-relatlimab. BRAF inhibitors may however be used as a second-line treatment in a post-IO treatment setting for those patients with *BRAF* V600 mutation, either in combination with a MEK inhibitor, or as a monotherapy (Section B.2.6.4).

Further guidelines for the management of untreated unresectable or metastatic melanoma include the European Society for Medical Oncology (ESMO) guidelines, the National Comprehensive Cancer Network (NCCN) guidelines and the American Society of Clinical Oncology (ASCO) guidelines, all of which also recommend immunotherapy as a first-line treatment.[38-40] Each of the guidelines also specify that nivolumab + ipilimumab is the preferred treatment of the immunotherapies, or that nivolumab + ipilimumab provides the most efficacious response when compared with nivolumab or pembrolizumab monotherapy.

Table 5 presents the key comparator treatment options available for patients with untreated unresectable or metastatic melanoma, as per the NICE guidelines.

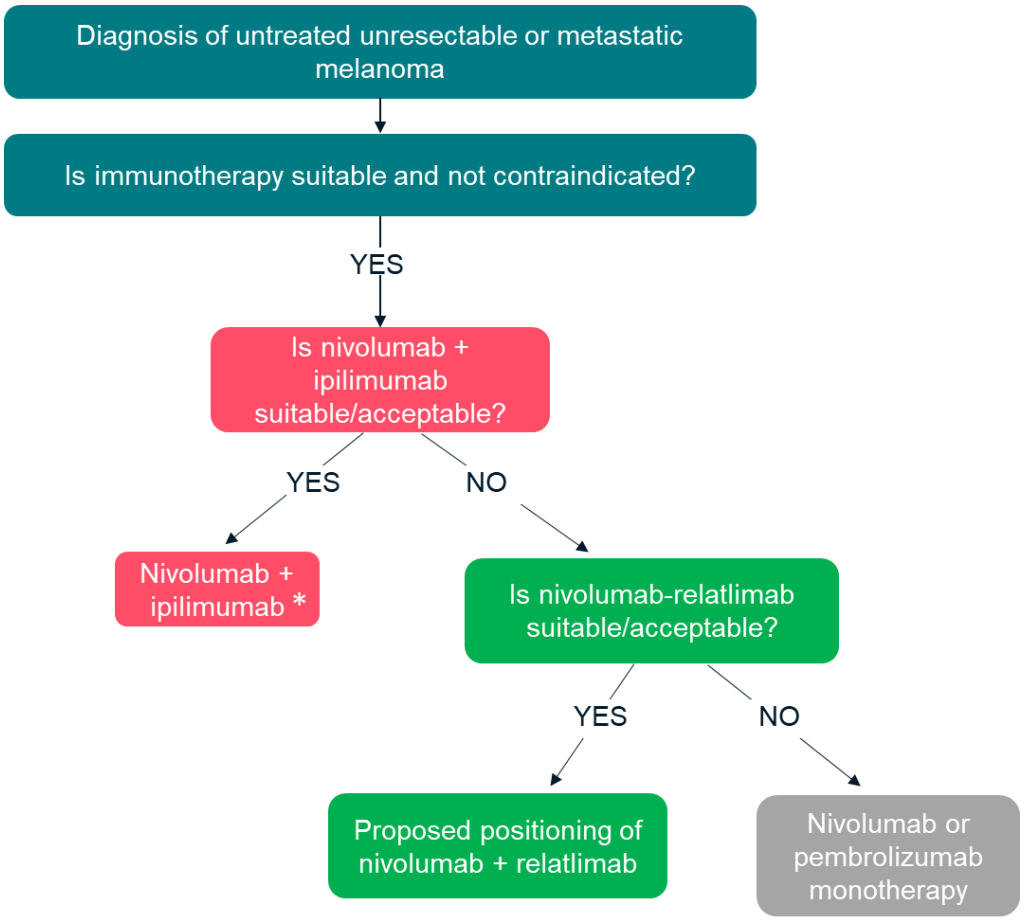
Table 5: Key comparators for the management of untreated unresectable or metastatic melanoma in England

Product (brand)	Treatment class	Dosing regimen	Market authorisation	NICE recommendation
Nivolumab (Opdivo®) + ipilimumab (Yervoy®)	Nivolumab: PD-1 checkpoint inhibitor Ipilimumab: CTLA4 checkpoint inhibitor	Nivolumab: 1 mg/kg every 3 weeks for a total of 4 doses Ipilimumab: 3 mg/kg every 3 weeks for a total of 4 doses Maintenance: nivolumab 480 mg every 4 weeks	Indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults	TA400: Nivolumab in combination with ipilimumab is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults, only when the company provides ipilimumab with the discount agreed in the patient access scheme.[41]
Pembrolizumab monotherapy (Keytruda®)	PD-1 checkpoint inhibitor	400 mg every 6 weeks	Indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma	TA366: Pembrolizumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma that has not been previously treated with ipilimumab, in adults, only when the company provides pembrolizumab in line with the commercial access agreement with NHS England.[42]
Nivolumab monotherapy (Opdivo®)	PD-1 checkpoint inhibitor	480 mg every 4 weeks	Indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults	TA384: Nivolumab as monotherapy is recommended, within its marketing authorisation, as an option for treating advanced (unresectable or metastatic) melanoma in adults.[43]
Key: CTLA-4, Cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed cell death-1. **Source:** nivolumab SmPC[44]; pembrolizumab SmPC[45]; ipilimumab SmPC[46] NICE TA400[41]; NICE TA366[42]; NICE TA384.[43]				

Figure 2 presents the current treatment pathway for patients with untreated unresectable or metastatic melanoma as per the NICE melanoma guidelines, and the anticipated positioning of nivolumab-relatlimab.

Nivolumab-relatlimab will provide an additional treatment choice to patients with untreated unresectable or metastatic melanoma and should facilitate broader access to dual IO therapy due to an improved safety profile compared with nivolumab + ipilimumab (Section B.2.9). Dual IO therapy is the preferred first-line treatment choice when suitable, due to an improved efficacy profile compared with IO monotherapy.[35, 47] On consultation, UK clinicians expressed the opinion that nivolumab-relatlimab may be a good alternative in patients either unfit to receive nivolumab + ipilimumab, or in centres without the capacity or experience to manage potential toxicities that arise from treatment with nivolumab + ipilimumab. Therefore, clinicians anticipated nivolumab-relatlimab to be used initially in patients who are currently receiving IO monotherapy.[37]

Figure 2: Clinical pathway of care for patients with untreated unresectable or metastatic melanoma and the proposed positioning of nivolumab-relatlimab



Notes: *Clinicians noted that nivolumab-relatlimab may be a good alternative for some patients who are currently considered unfit for receive nivolumab + ipilimumab, or in centres without the capacity or experience to manage potential toxicities that arise from treatment with nivolumab + ipilimumab.
Source: Adapted from the NICE melanoma guidelines (2022)[36]

B.1.3.4.2. Unmet clinical need

Melanoma is responsible for approximately 90% of all skin-cancers deaths, with the most frequent cause of mortality being distant metastases, which occur in a rapid and overwhelming progression due to a combination of factors involving inherited genetics and tumorigenesis.[10]

The introduction of dual checkpoint inhibitors to the treatment landscape have demonstrated improved efficacy when compared with IO monotherapy. Table 6 presents the 1-year, 2-year, 5-year and 7.5-year overall survival rates of patients with advanced melanoma who received treatment with either nivolumab + ipilimumab or nivolumab monotherapy, as demonstrated in the CheckMate-067 trial. The 7.5-year overall survival (OS) rate was 48% for patients receiving nivolumab +

ipilimumab and 42% for patients receiving nivolumab monotherapy.[35] Although this data demonstrates improved survival rates compared with IO monotherapy, nivolumab + ipilimumab is associated with additional toxicity, and, consequently, not all patients with advanced melanoma are suitable candidates for nivolumab + ipilimumab due to their possible inability to withstand the toxicity.[36, 37] Patients who are ineligible or not deemed fit for dual IO therapy cannot benefit from the potential for better efficacy outcomes associated with this therapy and instead receive treatment that results in lower survival rates.[48, 49]

Table 6: OS rates of patients with advanced melanoma receiving nivolumab + ipilimumab and nivolumab monotherapy in CheckMate-067

	Nivolumab + ipilimumab (n = 314)	**Nivolumab monotherapy (n = 316)**
1-year survival rate	73%	74%
2-year survival rate	64%	59%
5-year survival rate	52%	44%
7.5-year survival rate	48%	42%
Key: OS, overall survival. **Source:** Larkin et al. 2017[50]; Larkin et al. 2019[15]; Hodi et al. 2022[35].		

As the choice of IO treatment is multifaceted and individualised to the patient, having a greater number of treatment options will be of true benefit to the patient.[37] There is currently a need for additional novel treatments that are able to provide comparable efficacy outcomes to the options currently available, with a more tolerable safety profile. Ultimately, an optimised risk–benefit profile would enable a higher proportion of patients with advanced melanoma the opportunity to benefit from more efficacious treatment.

B.1.4. Equality considerations

No equality considerations relating to the use of nivolumab-relatlimab have been identified or are anticipated.

B.2. Clinical effectiveness

Summary of key points:

Study identification

- An SLR identified one RCT study (RELATIVITY-047) that provided direct efficacy and safety evidence for nivolumab-relatlimab
- RELATIVITY-047 is a Phase 2/3, multicentre, randomised, double-blind controlled trial evaluating the efficacy and safety of combined LAG-3 and PD-1 inhibition with nivolumab-relatlimab compared with nivolumab in patients with previously untreated unresectable or metastatic melanoma[47]

Efficacy

- At the October 2022 database lock (median follow-up of [redacted] months), nivolumab-relatlimab demonstrated superior efficacy when compared with nivolumab:
  - Median progression-free survival (PFS) by blinded independent central review (BICR): [redacted] months versus [redacted] months (hazard ratio [HR] [redacted]; 95% confidence interval [CI]: [redacted], [redacted])[51]
  - Median OS: not reached (NR) versus [redacted] months (HR [redacted]; 95% CI: [redacted], [redacted])[51]
- Nivolumab-relatlimab demonstrated superior efficacy compared with nivolumab across key pre-specified subgroups, irrespective of PD-L1 and LAG-3 status, AJCC metastatic stage and *BRAF* mutational status[51]
- Both a time-varying network meta-analysis (NMA) and an indirect treatment comparison (ITC) adjusting for differences in baseline characteristics have been conducted. Both demonstrate that nivolumab-relatlimab has similar efficacy to nivolumab + ipilimumab in terms of OS and PFS among adults with previously untreated unresectable or metastatic melanoma
- The NMA also demonstrated that, when compared to pembrolizumab, nivolumab-relatlimab provides statistical improvement in PFS from month 3 onwards, and a numerical, but not statistically significant, advantage in OS at all timepoints

Safety

- The safety profile of nivolumab-relatlimab in the RELATIVITY-047 trial was manageable and consistent with the known mechanisms of action of immune checkpoint inhibitors[51]
- No new safety signals or new types of clinically important events were identified when compared with nivolumab[51]
- As of the October 2022 database lock, [redacted] patients in the nivolumab-relatlimab arm and [redacted] patients in the nivolumab arm experienced treatment-related deaths[51]
- As demonstrated by the NMA and adjusted ITC, the safety profile of nivolumab-relatlimab appeared favourable compared with that of nivolumab-ipilimumab

B.2.1. Identification and selection of relevant studies

An SLR was conducted to identify and select RCT evidence on the efficacy and safety of systemic therapies for patients with untreated unresectable or metastatic melanoma. A total of 121 citations were identified, reporting on 16 unique trials. This SLR covered a broad range of interventions, including BRAF inhibitors which are not listed within the final scope (Table 1). The results of the SLR were therefore further refined to align with the decision problem presented in this submission. Of the 16 unique trials, four were relevant to the decision problem.

RELATIVITY-047 was the only trial to provide direct evidence for nivolumab-relatlimab in the treatment of untreated unresectable or metastatic melanoma; the trial methodology and results are presented in the following sections.

The results of the remaining three trials were utilised for indirect treatment comparisons, as presented in Section B.2.9. Full details on the SLR are provided in Appendix D.

Table 7: List of included studies relevant to the decision problem

Trial	Interventions	Study design	Patient population	Reference
RELATIVITY-047	• Nivolumab-relatlimab	International, Phase II/III,	Patients with previously	Lipson et al., 2021[52]

Trial	Interventions	Study design	Patient population	Reference
	(nivolumab 480 mg + relatlimab 160 mg Q4W) • Nivolumab monotherapy (3 mg/kg)	randomised, double-blind trial	untreated metastatic or unresectable melanoma (Stage III or IV)	
CheckMate-067	• Ipilimumab monotherapy (3 mg/kg) • Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) • Nivolumab monotherapy (3 mg/kg)	International, Phase III, randomised, double-blind trial	Patients with previously untreated unresectable or metastatic melanoma (Stage III or IV)	Larkin et al., 2015[53]
CheckMate-069	• Ipilimumab monotherapy (3 mg/kg) • Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg)	International, Phase II, randomised, double-blind trial	Patients with previously untreated unresectable or metastatic melanoma (Stage III or IV)	Postow et al., 2015[54]
KEYNOTE-006	• Ipilimumab monotherapy (3 mg/kg) • Pembrolizumab monotherapy (10 mg/kg)	International, Phase III, randomised, open-label trial	Patients with unresectable or metastatic melanoma (Stage III or IV)	Robert et al., 2015[55]
Key: IO, immuno-oncology; Q4W, every four weeks; RCT, randomised controlled trial; SLR, systematic literature review.				

B.2.2. List of relevant clinical effectiveness evidence

The RELATIVITY-047 trial is the pivotal source of data for nivolumab-relatlimab in this submission. A summary of the RELATIVITY-047 trial is presented in Table 8.

All efficacy and safety data presented for the RELATIVITY-047 trial are taken from the October 2022 database lock, unless otherwise stated/referenced.[51] This data-cut provides a minimum follow-up of [redacted] months and a median follow-up duration of [redacted] months (range: [redacted], [redacted] months), specifically [redacted] months in the nivolumab-relatlimab arm and [redacted] months in the nivolumab arm.

Table 8: RELATIVITY-047

Trial	**RELATIVITY-047**
Trial title	A Randomised, double-blind Phase 2/3 Study of Relatlimab combined with Nivolumab versus Nivolumab in participants with previously untreated metastatic or unresectable melanoma
Trial number	NCT03470922
Study design	Phase II/III, randomised, double-blind controlled trial
Population	Patients with previously untreated metastatic or unresectable melanoma
Intervention(s)	Relatlimab 160 mg + nivolumab 480 mg (IV Q4W)
Comparator(s)	Nivolumab 480 mg (IV Q4W)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in the model	*N/A*
Reported outcomes specified in the decision problem	• **Progression-free survival** • **Overall survival** • Response rates • **Adverse effects of treatment** • Health-related quality of life
All other reported outcomes	• **Time on treatment** • **Subsequent therapies**
Key publication	Tawbi et al. 2022 (Primary publication; database lock: March 2021)[47]
Secondary sources	Long et al. 2022[56] (ASCO Plenary Series; database lock: October 2021) Lipson et al. 2021[52] (ASCO Annual meeting; database lock: March 2021) Schadendorf et al. 2021[57] (Society of Melanoma Research; database lock: March 2021)
Key: ASCO, American Society of Clinical Oncology; IV, intravenous; Q4W, every 4 weeks. **Notes:** Bolded outcomes represent those directly used in the economic model. **Source:** RELATIVITY-047 clinical study report (primary analysis)[58]	

B.2.3. Summary of methodology of RELATIVITY-047

B.2.3.1. Study design

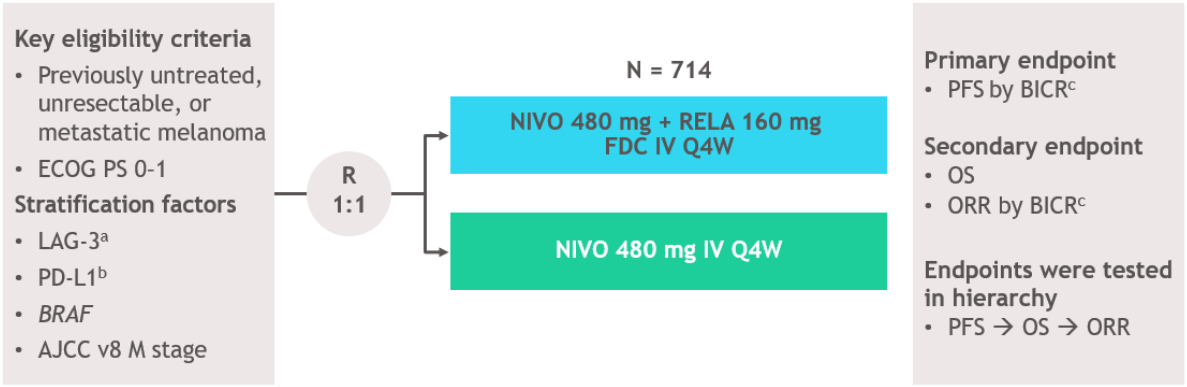
The RELATIVITY-047 trial is an ongoing, international, Phase II/III, double-blind randomised trial evaluating the FDC of the LAG-3 and PD-1 checkpoint inhibitors

nivolumab and relatlimab compared with nivolumab monotherapy in patients with previously untreated metastatic or unresectable melanoma.

A schematic of the trial design is presented in Figure 3.

Patients were randomly assigned in a 1:1 ratio to receive either 160 mg relatlimab and 480 mg nivolumab in a FDC, or 480 mg nivolumab. Both therapies were administered in a single 60-minute IV infusion Q4W (every 4 weeks).

Figure 3: RELATIVITY-047 trial design



Key: AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; FDC, fixed dose combination; IV, intravenous; LAG-3, lymphocyte-activation gene-3; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q4W, every 4 weeks; R, randomised.
Notes: a, LAG-3 expression on immune cells (1%) determined by analytically validated IHC assay (Labcorp, Burlington, NC, USA); b, PD-L1 expression on tumour cells (1%) determined by validated Agilent Dako PD-L1 IHC 28-8 pharmDx test (Agilent, Santa Clara, CA, USA); c, First tumour assessment (RECIST v1.1) performed 12 weeks after randomisation, every 8 weeks up to 52 weeks, and then every 12 weeks.
Source: Long et al. 2022[56]

Within the RELATIVITY-047 trial, patients continued to receive treatment with nivolumab-relatlimab or nivolumab until disease progression, unacceptable toxicity, withdrawal of consent, or end of the trial. Treatment beyond the initial progression was permitted if the investigators assessed that the patient had clinical benefit and if the patient did not have unacceptable side effects. Although IO treatments have a specified 2-year stopping rule in specific indications, it is not compulsory for patients receiving IO treatment for melanoma.[37] Consultation with UK clinical experts confirmed that the vast majority of patients in UK clinical practice will stop treatment after 2 years, with less than 10% of patients continuing treatment beyond this time

point.[37] It was noted that treatment decisions to continue or stop at 2 years would be clinically based, i.e. if they expected that the patients would continue to benefit from treatment, how well they tolerated treatments, with patient preference being a small driver.

Stratification factors at randomisation were as follows:

- Tumour PD-L1 expression (≥ 1% versus < 1%)
- LAG-3 expression (≥ 1% versus < 1%)
- *BRAF* mutation (V600 mutation positive versus V600 wild-type)
- AJCC v8 metastatic stage (M0 or M1 with normal LDH levels versus M1 with elevated LDH levels)

Table 9 presents an overview of the methodology of the RELATIVITY-047 trial.

Table 9: Summary of the RELATIVITY-047 trial methodology

Trial name	RELATIVITY-047
Trial design	Phase II/III, randomised, double-blind trial
Location	114 sites in 25 countries, including: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, New Zealand, Norway, Poland, Romania, Russian Federation, Spain, Sweden, the UK and the US
Key eligibility criteria for patients	**Inclusion criteria:** • Males and females ≥ 12 years of age • Histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the 8th edition of the AJCC staging system • No prior systemic anti-cancer therapy for unresectable or metastatic melanoma, but prior adjuvant or neoadjuvant melanoma therapy with a specified regimen was allowed (anti-PD-1, anti-CTLA-4, or BRAF-MEK containing regimen if ≥ 6 months between last dose and date of recurrence; interferon with last dose ≥ 6 weeks before randomisation) • ECOG performance status of 0 or 1, or a Lansky performance score ≥ 80% for minors • Known *BRAF* V600 mutation status or consent to *BRAF* V600 mutation testing per local institutional standards during the screening period **Exclusion criteria:** • Active or untreated brain or leptomeningeal metastases

Trial name	RELATIVITY-047
	• Uveal melanoma • Active autoimmune disease or condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment • History of myocarditis The full eligibility criteria is presented in Appendix N.
Settings and locations where the data were collected	A total of 714 patients were enrolled and treated at one of the 114 trial sites.
Trial drugs	**Investigational arm: Nivolumab-relatlimab** Patients received a solution for injection of nivolumab (480 mg) + relatlimab (160 mg) every 4 weeks, prepared in normal saline **Comparator arm: Nivolumab monotherapy** Patients received a solution for injection of nivolumab (480 mg) every 4 weeks, prepared in normal saline Nivolumab +relatlimab and nivolumab monotherapy were administered as ~60 minute IV infusions. No dose reductions or escalations were permitted for either treatment arm.
Permitted and disallowed concomitant medication	Patients were permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed type hypersensitivity reaction caused by a contact allergen) is permitted. The following medications are prohibited during the trial: • LAG-3-targeting agents • Any botanical preparation (e.g. herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalised locally • Immunosuppressive agents (except used to treat a drug-related AE) • Immunosuppressive doses of systemic corticosteroids • Any concurrent anti-neoplastic therapy (i.e. chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of malignancy) • Any live/attenuated vaccine (e.g. varicella, zoster, yellow

Trial name	RELATIVITY-047
	fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) during treatment and until 100 days after last dose. Inactivated vaccines are permitted.
Primary endpoints	• PFS, as assessed by BICR using RECIST v1.1
Other outcomes used in the economic model/specified in the scope	• OS • ORR as assessed by BICR • DOR • AEs
Other outcomes of interest	• Subsequent therapies • HRQL
Pre-planned subgroups	• Subgroups were prespecified, which included the stratification factors of LAG-3 expression, PD-L1 status, *BRAF* status and AJCC v8 metastatic stage • Subgroups were examined for the primary endpoint of PFS and secondary endpoints of OS, ORR and DOR

Key: AE, adverse events; AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; LAG-3, lymphocyte-activation gene-3; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: RELATIVITY-047 clinical study report (primary analysis)[58]

B.2.3.2. Outcomes reported

The primary endpoint of the RELATIVITY-047 trial was progression-free survival (PFS) by BICR, and the key secondary endpoints were OS and objective response rate (ORR). A detailed summary of the trial endpoints, their definitions and censoring rules is presented in Appendix N.

HRQL was evaluated prior to dosing in each 4-week treatment cycle using the Functional Assessment of Cancer Therapy-melanoma (FACT-M) questionnaire and the EQ-5D-3L questionnaire.[59, 60] The FACT-M questionnaire includes the four FACT-general (FACT-G) subscales of physical, social/family, emotional, and functional well-being, in addition to the FACT-M melanoma subscale and a melanoma surgery scale.[60] Change from baseline in each HRQL score was analysed at time points with ≥ 10 patients using a mixed model for repeated measurements, with randomisation strata, treatment, visit, and baseline HRQL score considered. Clinically meaningful changes from baseline were determined using prespecified minimally important differences (MIDs).[59, 61]

B.2.3.3. Baseline demographics and disease characteristics

The baseline demographics and disease characteristics for the intention-to-treat (ITT) population of the RELATIVITY-047 trial are presented in Table 10.

The patient population enrolled in RELATIVITY-047 is considered representative of that seen within UK clinical practice, as confirmed by UK clinicians.[37] Further discussion on the generalisability of the trial is provided in Section B.2.12.1.1.

The baseline patient demographics and disease characteristics were well balanced between the treatment arms. Compared with the nivolumab arm, a higher proportion of patients in the nivolumab-relatlimab arm had AJCC (8th edition) metastatic Stage M1c disease (42.5% versus 35.4%), which is a poorer prognostic factor relative to lower-stage disease.[47] The nivolumab-relatlimab arm also had a higher proportion of patients with three or more sites with at least one lesion (31.5% versus 24.2%).

The stratification factors of PD-L1 and LAG-3 status and *BRAF* mutational status were also well-balanced between treatment arms. Efficacy results stratified by these factors are presented in Section B.2.7.

A total of 60 patients received adjuvant or neoadjuvant treatment prior to enrolment, of which interferon was the most common treatment given in both the nivolumab-relatlimab and nivolumab arms at 6.5% and 6.1%, respectively.[47] Of note, patients were not enrolled into the RELATIVITY-047 trial if they had received prior systemic anti-cancer therapy for unresectable or metastatic melanoma but could be enrolled if they received prior adjuvant or neoadjuvant melanoma therapies, and all related AEs had either returned to baseline or stabilised.

Table 10: Baseline demographics and disease characteristics (ITT population)

Characteristic	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
Median age (range), years	63 (20, 94)	62 (21, 90)
Female, n (%)	145 (40.8)	153 (42.6)
Previous systemic therapy regimen, n (%)		
Adjuvant	31 (8.7)	26 (7.2)
Neoadjuvant	2 (0.6)	1 (0.3)
Unknown or other	0	2 (0.6)

Characteristic	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
Type of systemic therapy, n (%)		
CLTA-4 inhibitor	5 (1.4)	2 (0.6)
PD-1 inhibitor	4 (1.1)	1 (0.3)
Combination of CLTA-4 and PD-1 inhibitors	1 (0.3)	0 (0.0)
Combination of BRAF and MEK NRAS inhibitor	1 (0.3)	1 (0.3)
Interferon	23 (6.5)	22 (6.1)
AJCC v8 metastatic stage, n (%)		
M0	35 (9.9)	23 (6.4)
M1A	77 (21.7)	107 (29.8)
M1B	85 (23.9)	88 (24.5)
M1C	151 (42.5)	127 (35.4)
M1D	6 (1.7)	11 (3.1)
Melanoma subtype classification, n (%)		
Cutaneous acral	41 (11.5)	41 (11.4)
Cutaneous non-acral	249 (70.1)	254 (70.8)
Mucosal	23 (6.5)	28 (7.8)
Other	42 (11.8)	36 (10.0)
ECOG PS, n (%)		
0	236 (66.5)	242 (67.4)
1	119 (33.5)	117 (32.6)
Serum LDH level, n (%)		
> ULN	130 (36.6)	128 (35.7)
> 2 x ULN	32 (9.0)	31 (8.6)
Tumour burden[a], median (range), mm	59.0 (10, 137)	54.5 (10, 548)
Sites with ≥ 1 lesion, n (%)		
1	127 (35.8)	158 (44.0)
2	111 (31.3)	102 (28.4)
≥ 3	112 (31.5)	87 (24.2)
Stratification factors, n (%)		
LAG-3 expression		
≥ 1%	268 (75.5)	269 (74.9)
< 1%	87 (24.5)	90 (25.1)
PD-L1 expression		
≥ 1%	146 (41.1)	147 (40.9)
< 1%	209 (58.9)	212 (59.1)
BRAF mutation status		
Patients with *BRAF* mutations	136 (38.3)	139 (38.7)
Patients without *BRAF* mutations	219 (61.7)	220 (61.3)
AJCC M stage		
M0, M1 and normal LDH level	232 (65.4)	237 (66.0)

Characteristic	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
M1 and elevated LDH level	123 (34.6)	122 (34.0)

Key: AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention to treat; LAG-3, lymphocyte-activation gene-3; LDH, lactate dehydrogenase; PD-L1, programmed cell death-ligand 1; ULN, upper limit of normal.
Notes: [a] Sum of reference diameters of target lesions in mm.
Source: Tawbi et al. 2022[47]; Long et al. 2022[56]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. Analysis sets

The main analysis population sets in the RELATIVITY-047 trial are presented and defined in Table 11. The primary endpoint was performed on the randomised analysis set, herein referred to as the ITT analysis set. Of note, the ITT (randomised) analysis set is the same as the treated analysis set as all randomised patients received at least one dose of the double-blinded trial drug. Safety analyses were performed using the ITT analysis set.

Table 11: RELATIVITY-047 analysis sets

Analysis set	Definition	Number of patients		
		Nivolumab-relatlimab	Nivolumab	Total
Enrolled	All patients who sign informed consent and were registered into the trial	-	-	1281
Randomised (ITT)	All patients who are randomised to any treatment group	355	359	714
Treated	All patients who received at least one dose of double-blind trial medication	355	359	714
Biomarker	All randomised patients with available biomarker data			
	LAG-3 quantifiable	[redacted]	[redacted]	[redacted]
	PD-L1 quantifiable	[redacted]	[redacted]	[redacted]
	PD-L1 non-quantifiable	[redacted]	[redacted]	[redacted]

Key: ITT, intention-to-treat; LAG-3, lymphocyte-activation gene-3; PD-L1, programmed cell death-ligand 1.
Source: RELATIVITY-047 statistical analysis plan[62]; RELATIVITY-047 clinical study report (primary analysis)[58]

B.2.4.2. Statistical analyses

A summary of the statistical methods used in the RELATIVITY-047 trial are presented in Table 12.

Table 12: Summary of statistical analyses

Hypothesis objective	Treatment with nivolumab-relatlimab will improve PFS when compared with nivolumab monotherapy in previously untreated patients with unresectable or metastatic melanoma.
Statistical analysis	Type I error control across endpoints was performed hierarchically. If the primary analysis of PFS was significantly superior, then the secondary endpoints would be tested in the order of OS followed by ORR. That is, if the results comparing PFS between treatment groups were significant at the applicable alpha level, then results comparing OS between treatment groups were to be interpreted. If the results comparing OS between treatment groups were significant, then results comparing ORR between treatment groups were to be interpreted upon data maturity after all randomised subjects have the potential for 7 months of follow-up. Other endpoints were not formally tested. Unless otherwise noted, discrete variables are tabulated by the frequency and proportion of patients falling into each category, grouped by treatment. Percentages given in these tables will be rounded to the first decimal and, therefore, may not always sum to 100%. Percentages less than 0.1 will be indicated as '< 0.1'. Continuous variables will be summarised by treatment group using the mean, standard deviation, median, minimum, and maximum values. Time-to-event variables (e.g. time to resolution) were analysed using the Kaplan–Meier technique. When specified, the median will be reported along with 95% CI using Brookmeyer and Crowley method (using log-log transformation for constructing the confidence intervals). Adverse events will be categorised using the most current version of Medical Dictionary for Regulatory Activities (MedDRA), by system organ class and preferred term. Prior therapies will be summarised using the most current version of the WHO drug dictionary. Statistical analyses will be carried out in SAS, unless otherwise indicated.
Sample size, power calculation	The sample size was calculated in order to compare PFS among subjects randomised to receive nivolumab-relatlimab vs nivolumab monotherapy. The number of events required was simulated based on results from CheckMate 067 with a median PFS of 6.9 months for the nivolumab monotherapy arm and 11.8 months for the nivolumab-relatlimab arm.[63] The cure rates were assumed to be 30% In the nivolumab monotherapy arm and 40% in the nivolumab-relatlimab arm. The power is also affected by non-proportional hazards, since it is driven by the number of events, not the number of patients, and some fraction of the patients in each arm are assumed to remain event-free for the duration of the study. Based on these assumptions, the study required at least 365 PFS events to ensure approximately 85% power to detect a HR of 0.73 with an overall Type I error of 0.05. Approximately 700 patients were to be randomised to the two treatment arms in a 1:1 ratio. The final PFS

	analysis was planned to occur when 365 patients had a PFS event per BICR. This was expected at approximately 34 months.
Data management, patient withdrawals	In general, missing data was not imputed for the purpose of data analysis, unless otherwise specified. The rules for censored data for PFS and OS are defined in Appendix N.1.2.
Data-cuts and statistical analysis timepoints	An interim analysis was conducted by the DMC, to determine whether the HR in the analysis of PFS met the prespecified threshold of ≤ 0.8. The prespecified threshold was met and the trial proceeded. The trial investigators and sponsors were unaware of the results of the interim analysis. The clinical database was locked for the planned formal PFS primary analysis on the 9 March 2021. Efficacy results for this data-cut are presented in the primary publication Tawbi et al. 2022.[47] This data-cut provided a median follow-up of 13.2 months. A further database lock was conducted on October 2021, providing a minimum follow-up of [redacted] months and a median follow-up of 19.3 months. Efficacy results for this data-cut are presented at ASCO (Long et al. 2022[64]) All data presented in this submission are from the most recent data-cut (October 2022), unless otherwise stated/referenced.
Key: ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CI, confidence interval; DMC, data monitoring committee; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; WHO, World Health Organization. **Source:** Tawbi et al. 2022[47]; RELATIVITY-047 statistical analysis plan[62]; RELATIVITY-047 clinical study report (primary analysis).[58]	

B.2.4.3. Patient flow

Patient disposition data for the RELATIVITY-047 trial are presented in Appendix D, alongside a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient flow.

In summary, 1,281 patients were enrolled in the trial, of which 714 were randomly assigned to receive nivolumab-relatlimab (n = 355) or nivolumab (n = 359).[47] All patients received at least one dose cycle of either nivolumab-relatlimab or nivolumab. At the time of the data cut-off (October 2022), [redacted] ([redacted]%) patients in the nivolumab-relatlimab arm and [redacted] ([redacted]%) patients in the nivolumab arm were still receiving treatment within the trial.[51] The primary reasons for discontinuation of treatment included disease progression (nivolumab-relatlimab: n = [redacted] [[redacted]%]; nivolumab: n = [redacted] [[redacted]%]) and trial drug toxicity (nivolumab-relatlimab: n = [redacted] [[redacted]%]; nivolumab: n = [redacted] [[redacted]%]).[51]

A total of [redacted] ([redacted]%) patients in the nivolumab-relatlimab arm and [redacted] ([redacted]%) patients in the nivolumab arm were still continuing in the trial.[51] The primary reason for discontinuation of the trial was death (nivolumab-relatlimab: n = [redacted] ([redacted]%); nivolumab: n = [redacted] ([redacted]%).

The median treatment duration was [redacted] months in the nivolumab-relatlimab arm and [redacted] months in the nivolumab arm.[51] The median duration of follow-up was [redacted] months (range: [redacted], [redacted] months), specifically [redacted] months in the nivolumab-relatlimab arm and [redacted] in the nivolumab arm.

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and in accordance with the ethical principles originating from the Declaration of Helsinki and those underlying the European Union Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The quality assessment of the RELATIVITY-047 trial has been conducted using the Cochrane Collaboration's Risk of Bias tool. The overall risk of bias was considered to be low – full results of this assessment are presented in Appendix D.3.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. Primary endpoint: progression-free survival by blinded independent central review

Table 13 presents the results for PFS by BICR for the ITT population of the RELATIVITY-047 trial. In RELATIVITY-047, nivolumab-relatlimab became the first FDC immunotherapy to demonstrate superior PFS by BICR compared with nivolumab. The median PFS was [redacted] months (95% CI [redacted], [redacted]) with nivolumab-relatlimab, compared with [redacted] months (95% CI [redacted], [redacted]) with nivolumab (HR [redacted]; 95% CI [redacted], [redacted]).[51] The percentage of patients who had not progressed at 12

months was [redacted]% (95% CI [redacted], [redacted]) with nivolumab-relatlimab and [redacted]% (95% CI [redacted], [redacted]) with nivolumab.[51]

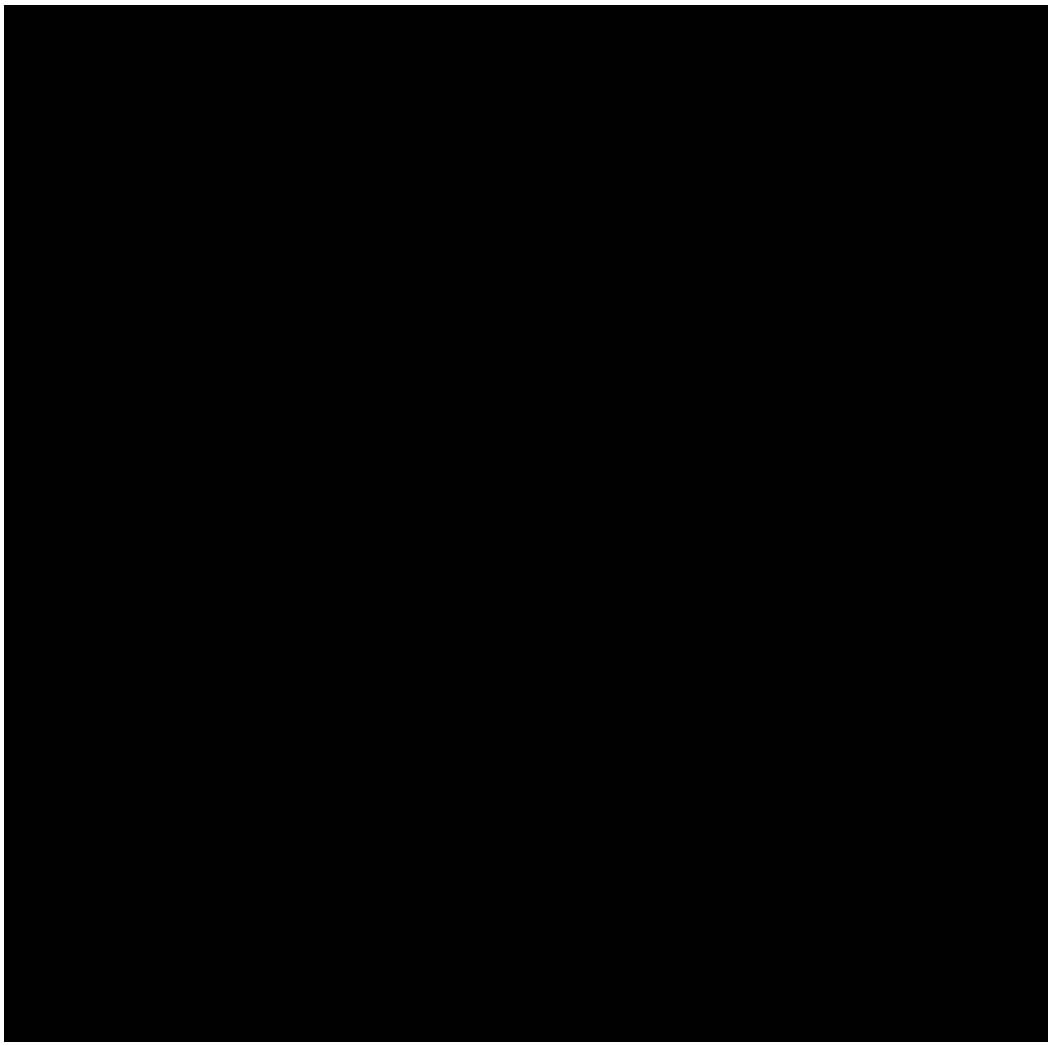
Table 13: Analysis of PFS by BICR in the RELATIVITY-047 trial (ITT population)

	Nivolumab-relatlimab (n = [redacted])	Nivolumab (n = [redacted])
Number of events	[redacted]	[redacted]
Median PFS (95% CI), months	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	
12-month PFS, % (95% CI)	[redacted]	[redacted]
24-month PFS, % (95% CI)	[redacted]	[redacted]
36-month PFS, % (95% CI)	[redacted]	[redacted]
48-month PFS, % (95% CI)	[redacted]	[redacted]

Key: BICR, blinded independent central review; CI, confidence interval; ITT, intention to treat; PFS, progression-free survival.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

As presented in Figure 4, the Kaplan–Meier (KM) curves for nivolumab-relatlimab and nivolumab separated by around Month 3 (i.e. the time of the first on-trial assessment) and remained separated through the follow-up period. The KM curve begins to plateau for both treatment arms at around 40 months, aligning with long-term data published from other immunotherapies (see Section B.3.3.2.1).

Figure 4: Kaplan–Meier Plot of PFS per BICR (primary definition; ITT population)



Key: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut).[51]

B.2.6.2. Secondary endpoints

B.2.6.2.1. Overall survival

Table 14 presents the results for OS for the ITT population of the RELATIVITY-047 trial.

As of the October 2022 data-cut, the median OS was [redacted] in the nivolumab-relatlimab arm, and [redacted] in the nivolumab arm. The OS at 24 and 48 months was [redacted]% and [redacted]%, respectively, in the nivolumab-relatlimab arm. These are higher

than the OS rates seen at 24 and 48 months in patients receiving nivolumab ([redacted]% and [redacted]%, respectively). Over the median follow-up of [redacted] months, [redacted] ([redacted]%) patients died in the nivolumab-relatlimab arm and [redacted] ([redacted]%) patients died in the nivolumab arm. Further information on patient deaths is provided in Section B.2.10.1.4.

Table 14: Analysis of OS in the RELATIVITY-047 trial (ITT population)

	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
Number of events	[redacted]	[redacted]
Median OS (95% CI), months	[redacted]	[redacted]
OS HR (95% CI)	[redacted]	
12-month OS, % (95% CI)	[redacted]	[redacted]
24-month OS, % (95% CI)	[redacted]	[redacted]
36-month OS, % (95% CI)	[redacted]	[redacted]
48-month OS, % (95% CI)	[redacted]	[redacted]

Key: ITT, intention to treat; OS, overall survival.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

The KM curve of OS is presented in Figure 5. The curves demonstrate an early and sustained separation, reflecting a persistent overall survival benefit with nivolumab-relatlimab compared to nivolumab.

Figure 5: Kaplan–Meier Plot of OS (ITT population)

Key: CI, confidence interval; OS, overall survival
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.6.2.2. Response rates

B.2.6.2.2.1. Objective response rate

Table 15 presents the results for the objective response rate (ORR) for the ITT population of the RELATIVITY-047 trial.

Nivolumab-relatlimab provides an improvement in the ORR compared with nivolumab. Among the patients who received nivolumab-relatlimab, the confirmed ORR was [redacted]% (95% CI: [redacted], [redacted]); of these, [redacted] ([redacted]%) patients had a complete response (CR), and [redacted] ([redacted]%) had a partial response (PR).[51] Comparatively, the ORR was [redacted]% (95% CI: [redacted], [redacted]) in the nivolumab arm; of these, [redacted] ([redacted]%) patients achieved a CR and [redacted] ([redacted]%) patients achieved a PR.

Table 15: Analysis of ORR in the RELATIVITY-047 trial (ITT population)

	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
ORR, n (% [95% CI])	[redacted]	[redacted]
Difference of ORR, % (95% CI)	[redacted]	
Odds ratio, % (95% CI)	[redacted]	
Confirmed BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
Non-CR/non-PD	[redacted]	[redacted]
PD, n (%)	[redacted]	[redacted]
Unable to determine, n (%)	[redacted]	[redacted]
Disease control rate, n (% [95% CI])	[redacted]	[redacted]

Key: BOR, best overall response; CI, confidence interval; CR, complete response; ITT, intention-to-treat; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.6.2.2.2. Duration of response

The median DOR was [redacted] for both treatment arms.[51] The proportion of patients with a DOR of at least 42 months was [redacted]. The median time to objective response was [redacted] months for both treatment arms.[51]

A detailed table of results and the Kaplan-Meier plot for the duration of response (DOR) is presented in Appendix N.2.1

B.2.6.3. Exploratory endpoints

The exploratory endpoints of PFS2 per investigator assessment and HRQL outcomes are presented in Appendix N.2.

B.2.6.4. Subsequent therapies

Table 16 presents a summary of the subsequent therapies used in patients in the ITT population of the RELATIVITY-047 trial.

The use of subsequent therapies was similar in both treatment arms, including the use of BRAF inhibitors as a monotherapy or in combination with MEK inhibitors ([redacted]% of patients in the nivolumab-relatlimab arm and [redacted]% in the nivolumab arm)

and PD-1 or CTLA-4 inhibitors as monotherapy or in combination ([redacted]% of patients in the nivolumab-relatlimab arm and [redacted]% in the nivolumab arm).[51]

Of note, the primary definition of PFS accounted for subsequent therapy by censoring at the last available tumour assessment on or prior to the date of subsequent therapy. Further information on subsequent treatments is presented in Section B.3.5.4.1.

The mix of subsequent therapies received by patients who progressed in the RELATIVITY-047 trial generally aligns with current UK clinical practice, although the proportion of patients receiving non-ipilimumab IO therapy post-progression is likely to be higher in the UK clinical setting. UK clinical experts have confirmed that, once a patient progresses after receiving IO monotherapy or IO combination at first line, their *BRAF* gene mutation status is considered in determining the next treatment option.[37] Experts noted that the proportion of UK patients with BRAF mutant status was approximately 35–50%. For *BRAF* wild-type patients who progress on IO monotherapy, ipilimumab monotherapy is the standard of care in the UK, though this would only be considered if the patient was fit enough to tolerate the toxicity of the treatment. For *BRAF* mutant patients, BRAF targeted treatments were considered to be a treatment option. Clinicians also stated that entry into a clinical trial would also be considered, especially for BRAF wild-type patients.[37]

Table 16: Subsequent treatments from RELATIVITY–047

Subsequent therapy	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
Any subsequent therapy, n (%)[a]	[redacted]	[redacted]
Systemic therapy, n (%)	[redacted]	[redacted]
PD-L1 and/or CTLA-4 inhibitors	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]
Nivolumab monotherapy	[redacted]	[redacted]
Ipilimumab monotherapy	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]
Avelumab monotherapy	[redacted]	[redacted]
BRAF and/or *MEK* inhibitor therapies	[redacted]	[redacted]
Trametinib + Dabrafenib	[redacted]	[redacted]
Encorafenib + Binimetinib	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]

Subsequent therapy	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
Vemurafenib	[redacted]	[redacted]
Other	[redacted]	[redacted]
Radiotherapy, n (%)	[redacted]	[redacted]
Allowed on-treatment radiotherapy. n (%)	[redacted]	[redacted]
Surgery, n (%)	[redacted]	[redacted]
Allowed on-treatment surgery. n (%)	[redacted]	[redacted]

Key: CTLA-4, cytotoxic T lymphocyte associated protein-4; PD-L1,programmed cell death-ligand 1.
Notes: [a], Patients may have received > 1 subsequent therapy.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.7. Subgroup analysis

In order to minimise potential imbalances across treatment arms, four stratification factors were utilised in the RELATIVITY-047 trial: tumour PD-L1 expression (≥ 1% versus < 1%), LAG-3 expression (≥ 1% versus < 1%), *BRAF* mutation (V600 mutation positive versus V600 wild-type) and AJCC v8 metastatic stage (M0 or M1 with normal LDH levels versus M1 with elevated LDH levels).[65]

Figure 6 presents the forest plot for PFS by BICR and OS by pre-specified subgroups, including PD-L1 and LAG-3 status and *BRAF* mutational status. A forest plot OS and PFS by further pre-specified subgroups and a forest plot for ORR by all pre-specified subgroups are presented in Appendix E.1.

Nivolumab-relatlimab demonstrated superior efficacy compared with nivolumab across key subgroups, irrespective of PD-L1 and LAG-3 status, AJCC metastatic stage and *BRAF* mutational status.[51] Findings were consistent with outcomes presented for the overall population. These results further support the efficacy of nivolumab-relatlimab, the first dual IO therapy to synergistically target PD-L1 and LAG-3.

Figure 6: Forest plot of treatment effect on PFS by BICR and OS

Key: AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LAG-3, lymphocyte activation gene-3; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.8. Meta-analysis

As RELATIVITY-047 is the only head-to-head trial comparing nivolumab-relatlimab with nivolumab, a meta-analysis has not been performed. Treatment comparisons for nivolumab-relatlimab versus nivolumab + ipilimumab and nivolumab-relatlimab versus pembrolizumab are presented in Section B.2.9.

B.2.9. Indirect and mixed treatment comparisons

As there are currently no head-to-head data available for the comparison of nivolumab-relatlimab versus nivolumab + ipilimumab or for nivolumab-relatlimab

versus pembrolizumab in adults with untreated unresectable or metastatic melanoma, a NMA has been performed, as presented in Section B.2.9.1.

As BMS has access to patient-level data (PLD) for both nivolumab-relatlimab and nivolumab + ipilimumab, an ITC adjusting for baseline characteristics was explored in terms of both efficacy and safety endpoints in the ITT population. Details of the adjusted ITC are presented in Section B.2.9.2.

B.2.9.1. Network meta-analysis

The NMA was conducted from a global perspective and included a wide range of potential comparators. However, this submission only focuses on the results relevant to the decision problem specified in this appraisal, namely the comparison of nivolumab-relatlimab with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (herein referred to as nivolumab + ipilimumab), pembrolizumab, and nivolumab (Section B.2.9.1.2).

The target population of the NMA aligns with the decision problem: adult patients with previously untreated unresectable or metastatic melanoma, independent of *BRAF* mutation and PD-L1 status.

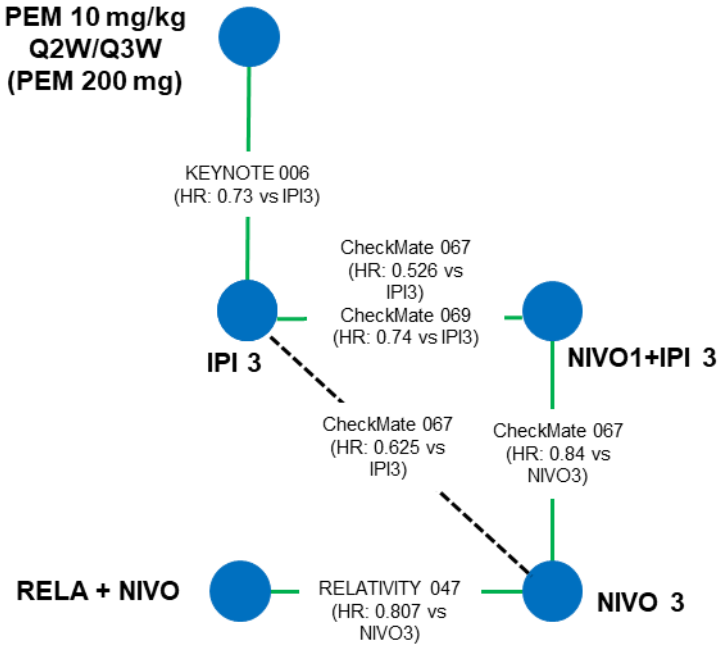
B.2.9.1.1. Methods of the NMA

B.2.9.1.1.1. Evidence base

As presented in Section B.2.1, an SLR was conducted to identify studies relevant for inclusion in the NMA. Of the studies included in the SLR, four trials were included in the network of evidence. An overview of these trials is presented in Table 7. Full details of the SLR search strategy, study selection process and results are presented in Appendix D.

Figure 7 presents the evidence network informing OS and PFS for the ITT population, comprising four studies assessing five interventions.

Figure 7: Network of evidence for IO trials



Key: HR, hazard ratio; IPI 3, ipilimumab 3 mg/kg; NIVO, nivolumab 480 mg; NIVO 1, nivolumab 1 mg/kg; NIVO 3, nivolumab 3 mg/kg; PEM, pembrolizumab 200 mg or 10 mg/kg every 2 weeks or every 3 weeks; RELA, relatlimab 160mg.
Note: Green line represents a trial that reports data for a population of mixed PD-L1 and *BRAF* mutational status. Black dashed line signifies that a comparison is available from trial publication, but it is irrelevant to the decision problem presented in this submission.

B.2.9.1.1.2. Methods of analysis and presentation of results

For the studies identified within the network of evidence, following a feasibility assessment they were deemed sufficiently similar. As such, they were synthesised by means of NMAs for the following outcomes of interest: OS, PFS, AEs (Grade 3–4), TRAEs (Grade 3–4), discontinuation due to AEs and discontinuation due to TRAEs.

A summary of the feasibility assessment is presented in Appendix D.4.1.1.

Time-to-event outcomes

Prior to performing the NMA, the Grambsch and Therneau test was used to assess the proportional hazards assumption within each trial for both OS and PFS.[66] This test indicated that there is uncertainty whether the proportional hazards assumption holds within all studies; notably, there is significant evidence that that proportional hazards assumption is violated within CheckMate-067 for OS and PFS (see Appendix D.4.1.2). Given the violation of the proportional hazards assumption,

fractional polynomial NMAs (which do not assume proportional hazards) were preferred, over the synthesis of constant HRs.[67, 68] For OS and PFS, the following competing survival distributions were considered using the multivariate NMA framework: Weibull, Gompertz, and second-order fractional polynomials including p1 = 0 or 1 and p2= -1, 0.5, 0, 0.5, or 1 (Model 9 and Model 10). Additional detail on the fractional polynomial methods is provided in Appendix D.4.1.3. Results of the time-varying NMA are presented in Section B.2.9.1.2. Analyses assuming constant HRs were also conducted; results of these analyses are presented in Appendix D.4.1.5.

Binary outcomes

Each of the safety and tolerability outcomes are binary outcomes. For these outcomes, the NMA was performed based on the proportion of patients experiencing the event of interest using a regression model with a binomial likelihood and logit link. Normal non-informative prior distributions for the parameters were used with a mean of 0 and a variance of 10,000. Relative treatment effects were expressed as odds ratios (ORs). Results from the safety analyses are presented in Section B.2.10.2.

Fixed- and random-effects models

Both fixed- and random-effects models were considered. In general, the assumptions of random-effects models are preferred as they are expected to be more plausible than those of fixed-effect models. However, as there was insufficient evidence available to estimate the between-study heterogeneity required to run the random-effects models, all the analyses were conducted using a fixed-effects model. The insufficiency was due to the availability of only a single trial for each treatment comparison in the evidence networks – with the exception of the comparison between nivolumab + ipilimumab and ipilimumab, which was informed by two trials (CheckMate 067 and CheckMate 069).

B.2.9.1.2. Time to event results

The results of the NMA were presented with estimates for treatment effects of each intervention relative to the reference treatment. The posterior distributions of relative treatment effects are summarised by the median and 95% credible intervals (CrIs),

which were constructed from the 2.5th and 97.5th percentiles of the posterior distributions. The HRs are presented for all times, t, between 0 and 82 months in graphical format, as well as in tabular format at 3-month intervals for the first year (12 months) and 6-month intervals thereafter, up until 48 months. The maximum value of 48 months reflects the maximum follow-up of RELATIVITY-047 in the most recent database lock (October 2022).

B.2.9.1.2.1. Progression-free survival

According to the model selection process, the best-fitting model was the second-order fractional polynomial ($P_1 = 0$, $P_2 = -1$, scale and 2nd shape). Results of the time-varying analysis for PFS are fully detailed in Table 17 and depicted in Figure 8 and Figure 9. Figure 8 illustrates cumulative survival over time for nivolumab-relatlimab and all competing interventions; this is achieved by applying HRs generated from the NMA to a reference modelled survival function using nivolumab 3 mg/kg as the reference treatment.

Results of the time-varying NMA of PFS indicated that there were no statistically significant differences in PFS between nivolumab-relatlimab and nivolumab + ipilimumab at any time point. Compared with pembrolizumab, nivolumab-relatlimab was associated with an improvement in PFS, the results of which were statistically significant at all timepoints except at Month 3. Nivolumab-relatlimab was also associated with an improvement in PFS compared with nivolumab, aligning with the PFS results presented for nivolumab-relatlimab versus nivolumab in the RELATIVITY-047 trial (Section B.2.6.1).

Table 17: Results of the fixed-effects fractional polynomial network meta-analysis for progression-free survival, presented as hazard ratios over time for nivolumab-relatlimab versus nivolumab + ipilimumab, pembrolizumab and nivolumab

Nivolumab-relatlimab versus	Time-varying HR (95% CrI)									
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Nivolumab + ipilimumab										
Pembrolizumab										
Nivolumab										

Key: CrI, credible interval; HR, hazard ratio.
Notes: Model presented is P1 = 0, P2 = -0.5, scale and 2nd shape, fixed effect. All bolded values are statistically significant at the 0.05 significance level

Figure 8: Results for the time-varying analysis of PFS, network for IO trials; cumulative survival over time

Key: IO, immuno-oncology; NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 9: Results for the time-varying analysis of PFS, network for IO trials; hazard ratios of nivolumab-relatlimab versus comparators

Key: IO, immuno-oncology;; NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

B.2.9.1.2.2. Overall survival

According to the model selection process (detailed in Appendix D.4.1.4), the best-fitting model for OS was the second-order fractional polynomial (P1=1, P2=-1, scale and 2nd shape). Results of the time-varying analysis are fully detailed in Table 18 and are depicted in Figure 10 and Figure 11. Figure 10 illustrates cumulative survival over time for nivolumab-relatlimab and all competing interventions; this is achieved by applying HRs generated from the NMA to a reference modelled survival function using nivolumab 3 mg/kg as the reference treatment. Notably, although analyses were conducted up to 48 months, not all comparators reported data up to this timepoint. Some of the

estimates, depicted with dashed lines in Figure 10 and Figure 11, are based on extrapolations and should be interpreted with caution where indicated.

Results of the time-varying NMA of OS indicated that there were no statistically significant differences observed between nivolumab-relatlimab and nivolumab + ipilimumab at any timepoint, with the point estimate of the HR remaining close to 1. When compared with nivolumab and pembrolizumab, treatment with nivolumab-relatlimab was associated with a numerical but not statistically significant advantage in OS at all timepoints. The OS results of the NMA comparison for nivolumab-relatlimab and nivolumab closely align with OS results presented from the RELATIVITY-047 trial (Section B.2.6.2.1).

Table 18: Results of the fixed-effects fractional polynomial network meta-analysis for overall survival, presented as hazard ratios over time for nivolumab-relatlimab versus nivolumab + ipilimumab, pembrolizumab and nivolumab

Nivolumab-relatlimab versus	Time-varying HR (95% CrI)									
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Nivolumab + ipilimumab	[redacted]									
Pembrolizumab	[redacted]									
Nivolumab	[redacted]									

Key: CrI, credible interval; HR, hazard ratio.
Notes: Model presented is P1 = 0, P2 = -0.5, scale and 2nd shape, fixed effect.

Figure 10: Results for the time-varying analysis of overall survival, network for IO trials; cumulative survival over time

Key: IO, immuno-oncology; NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 11: Results for the time-varying analysis of overall survival, network for IO trials; hazard ratios of nivolumab-relatlimab versus comparators

Key: IO, immuno-oncology; NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

B.2.9.1.3. Limitations of the meta-analysis

Due to insufficient data available, only fixed-effects analyses were performed. Given that fixed-effects analyses assume that there is no between-study heterogeneity, it is possible that uncertainty within the analysis may be underestimated.

For PFS, when reported, most trials evaluated the outcome based on investigator assessment though some used BICR. Evidence suggests there is a general concordance between survival by BICR and survival by investigator assessment, thus, the PFS NMA was not restricted based on how PFS was assessed.[69, 70]

The validity of the NMA also depends on the quality of included RCTs and the extent of any violations in the similarity and consistency assumptions across studies. In an NMA of RCTs involving multiple treatment comparisons, randomisation holds only within the individual trials and not across trials. If different direct comparisons show systematic differences in study and patient characteristics, and these differences are treatment effect modifiers, the estimates of any indirect comparison obtained via the NMA will be biased. To account for such bias, prior to conducting analyses, a feasibility assessment was conducted to assess heterogeneity related to study, patient, treatment, and outcome characteristics (Appendix D.4.1.1). Trials ultimately included in the SLR were considered homogeneous for suspected treatment effect modifiers. As presented in Figure 7, the NMA comparison of nivolumab-relatlimab and pembrolizumab utilises outputs from the KEYNOTE-006 trial. UK clinical experts have however expressed concerns around the generalisability of the KEYNOTE-006 trial to current UK clinical practice.[37] Specifically, KEYNOTE-006 was less reflective of the patient population of interest, with 34.2% of patients having previously received systemic treatment for advanced melanoma and 10.1% of patients presenting with brain metastases. This suggests that the relative treatment effects may therefore be underestimated compared with what is expected to be observed in UK clinical practice.

B.2.9.1.4. Conclusions

Results of the NMA suggest that, among adults with previously untreated unresectable or metastatic melanoma, nivolumab + ipilimumab may perform similarly to nivolumab-relatlimab in terms of OS and PFS. When compared with

pembrolizumab, nivolumab-relatlimab was shown to provide statistical improvement in PFS from Month 3 onwards, and a numerical, but not statistically significant, advantage in OS at all timepoints. Results for the comparison with nivolumab demonstrated that nivolumab-relatlimab was associated with a numerical advantage in PFS, which was statistically significant at Month 3, and OS, aligning with the OS and PFS results presented for the nivolumab-relatlimab and nivolumab comparison in RELATIVITY-047.

B.2.9.2. Adjusted indirect treatment comparison

B.2.9.2.1. Scope of the analysis

In the absence of head-to-head evidence comparing the efficacy of nivolumab-relatlimab directly with that of nivolumab + ipilimumab, a propensity score adjusted analysis (termed adjusted ITC) was performed. The adjusted ITC was conducted using PLD from the RELATIVITY-047 and CheckMate-067 trials to estimate the relative treatment effects of OS, PFS and safety outcomes in the ITT population. Table 7 provides a summary of RELATIVITY-047 and CheckMate-067. The analysis utilised an inverse probability of treatment (IPT) weighting approach to successfully address imbalances in the distribution of baseline characteristics between patients from the RELATIVITY-047 and CheckMate-067 trials; this analysis is hereafter referred to as the adjusted ITC.

Outcomes investigated in the ITC include the efficacy outcomes of PFS by investigator assessment and OS (Section 0); and safety outcomes of all-cause AEs, TRAEs, and TRAEs leading to discontinuation of treatment (Section B.2.10.2.2).

In RELATIVITY-047, the data used to inform the PFS and OS efficacy outcome comparisons and safety outcomes are from the October 2022 database lock, with a minimum follow-up of [redacted] and a median follow up of [redacted]. In CheckMate-067, outcomes were from the October 2020 database lock but were truncated to emulate the first per-protocol analysis of OS and to align with the median follow-up duration from RELATIVITY-047 trial. Patients in CheckMate-067 who did not experience an event by August 2016 were censored at this date. After truncation, the minimum and median follow-up in CheckMate-067 was 28 months and 29 months, respectively. In CheckMate-067, PFS per BICR data were only

available from the February 2015 database lock (minimum 9 months follow up), as this was not the primary endpoint definition of PFS. Therefore, a comparison of PFS per BICR were included in the current adjusted analyses, but were utilised data from the October 2021 database lock of RELATIVITY-047 only (minimum follow-up 9 months). The AEs in both trials were included in the analysis if they had occurred within the first 28 months of follow-up.

This propensity score adjusted ITC is strengthened by the similar inclusion and exclusion criteria used in both the RELATIVITY-047 and CheckMate-067 trials. A summary of the eligibility criteria for both trials is presented in Appendix D.4.2.1.

As individual PLD were available for both trials, an inverse probability treatment (IPT) weighting approach was implemented to address imbalances in the distribution of baseline characteristics between patients from the RELATIVITY-047 and CheckMate-067 trials. Summary statistics and distribution of IPT weights are presented in Appendix D.4.2.2.

The baseline factors included as predictors in the propensity score model are listed below. These baseline factors were selected based on data availability across the two trials and clinical input:

- Demographics
  - Age (continuous)
  - Sex (male versus female)
  - Geographic region
- Disease characteristics
  - ECOG performance status (≥ 1 versus 0)
  - Time from advanced melanoma diagnosis until randomisation (continuous, years)
  - Prior adjuvant therapy (yes versus no)
  - AJCC metastatic stage with LDH category 1 (M1any[1] versus M0/M1any[0])
  - AJCC disease stage at study entry (Stage III versus Stage IV)
  - Melanoma subtype (cutaneous acral versus cutaneous non-acral; mucosal versus cutaneous non-acral; other versus cutaneous non-acral)
  - *BRAF* mutation status (positive versus wild-type)

- Baseline LDH category 1 (> ULN versus ≤ ULN)
- Baseline LDH category 2 (> 2 x ULN versus ≤ 2 x ULN)
- PD-L1 expression category (≥ 1% versus < 1%/non-quantifiable)

The propensity score model was developed at the treatment arm level through binary logistic regression for nivolumab-relatlimab and nivolumab + ipilimumab in the ITT population, using a subset of patients with non-missing values. Each patient's weight was calculated as the inverse of the conditional probability of being exposed to a particular treatment arm given their baseline characteristics. The distribution of weights was evaluated for extreme values, defined as very large or very small values that are far from 1, by assessing the mean, SD, minimum, and maximum values. Truncation at the 5th and 95th percentiles was implemented in addition to stabilisation. The weighted distribution of patient characteristics was then compared between cohorts to ensure that they were balanced using standardised mean differences (SMDs). A threshold of SMD < 0.2 was used to indicate sufficient balance between the two treatment groups.

PFS and OS efficacy outcomes were estimated for the ITT population and were summarised using the KM method, and the median PFS and OS and corresponding 95% CIs were reported. HRs and 95% CIs were estimated for nivolumab-relatlimab relative to nivolumab + ipilimumab using a Cox proportional hazards model. Schoenfeld residuals were used to test the assumption of proportional hazards. Safety outcomes were also reported for the ITT population. All efficacy and safety outcomes from the primary analysis were reported before and after weighting.

Additionally, as an internal validation of the adjusted ITC between nivolumab-relatlimab and nivolumab + ipilimumab, the weighted nivolumab arms from both trials were compared for all safety and efficacy outcomes. These results are presented in Section B.2.9.2.2.3.

B.2.9.2.2. Results

The PFS per investigator assessment and OS curves before adjusting for baseline characteristics for the nivolumab-relatlimab versus nivolumab + ipilimumab comparison and for the nivolumab (RELATIVITY-047) versus nivolumab (CheckMate-067) comparison are presented in Appendix D.4.2.3.

B.2.9.2.2.1. Baseline characteristics after weighting

A summary of the baseline characteristics before and after weighting for nivolumab-relatlimab and nivolumab + ipilimumab is presented in Appendix D.4.2.3. After weighting, balance was achieved across the two treatment arms on all available baseline characteristics, apart from smoking status.

B.2.9.2.2.2. Efficacy results

There was no evidence of violation in the proportional hazards assumption for either PFS per investigator assessment or OS.

Figure 12 presents the PFS by investigator assessment after adjusting for baseline characteristics. An analysis with investigator-assessed PFS showed numerically higher hazard of progression or death for nivolumab-relatlimab than for nivolumab + ipilimumab (HR [redacted], 95% CI: [redacted], [redacted]), with the CI spanning 1. Results were consistent in the PFS per BICR analysis, which demonstrated that after weighting, nivolumab-relatlimab had similar hazard of progression or death (per BICR) as nivolumab + ipilimumab (HR = [redacted], 95% CI = [redacted], [redacted]).

Figure 12: Investigator-assessed PFS after weighting (ITT population)

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Figure 12 presents OS after adjusting for baseline characteristics. After weighting, median OS was not reached for both nivolumab-relatlimab (95% CI: [redacted] months, [redacted]) and nivolumab + ipilimumab (95% CI: [redacted] months, [redacted]). When comparing OS, nivolumab-relatlimab demonstrated a numerically lower risk of mortality compared with nivolumab + ipilimumab (HR [redacted]; 95% CI: [redacted], [redacted]), with the CIs spanning 1.

Figure 13: Overall survival after weighting (ITT population)

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.

B.2.9.2.2.3. Comparison of weighted nivolumab arms of RELATIVITY-047 and CheckMate-067

The weighed nivolumab arms from both RELATIVITY-047 and CheckMate-067 were compared for all safety and efficacy outcomes.

A summary of baseline characteristics before and after weighting for the nivolumab arms of CheckMate-047 and CheckMate-067 are presented in Appendix D.4.2.3. Following weighting, balance was achieved on all variables included in the propensity score model.

Figure 14 presents the PFS per investigator assessment following adjustment for baseline characteristics for the nivolumab arms of RELATIVITY-047 and CheckMate-067. An analysis using investigator-assessed PFS showed a similar hazard of progression or death for both nivolumab arms after weighting (HR [redacted], 95% CI: [redacted], [redacted]), with the point estimate of the HR close to 1 and the CI spanning 1.

Figure 14: PFS per investigator assessment after weighting (nivolumab arms of CheckMate-067 and RELATIVITY-047; ITT population)

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Figure 15 presents OS following adjustment for baseline characteristics for the nivolumab arms of RELATIVITY-047 and CheckMate-067. An analysis of OS showed a similar risk of mortality for both nivolumab arms after weighting (HR [redacted], 95% CI: [redacted], [redacted]), with the point estimate of the HR close to 1 and the CI spanning 1.

Figure 15: OS after weighting (nivolumab arms of CheckMate-067 and RELATIVITY-047; ITT population)

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

B.2.9.2.3. Limitations of the adjusted ITC

There are some factors in this study that should be considered when interpreting the results. Firstly, the weighting approach was limited to available baseline patient characteristics consistently reported across the two trials, and the propensity score model to patients with non-missing values for those characteristics. However, it should be noted that there was a high level of consistency in reported baseline characteristics across the two trials, and very few patients were excluded from the final analysis set as a result of missing values.

The adjusted ITC benefited from utilising PLD from both the RELATIVITY-047 and CheckMate-067 trials. After weighting, balance was assessed in the distribution of baseline characteristics using standard thresholds defined by the standardized mean differences (SMDs), and balance was achieved on all available baseline characteristics, with the exception of smoking status. However, for smoking status the SMD of 0.22 only marginally surpassed the threshold value of 0.20 and therefore this is not expected to have an impact on the findings. Indeed, the fact that balance

was successfully achieved after the weighting on all key prognostic factors included in the propensity score model strengthens the notion that the observed similarity in efficacy outcomes across the two arms can be attributed to an appropriate assessment of the relative treatment effect, as opposed to confounding.

It is acknowledged that there may be other important differences in the patient populations between RELATIVITY-047 and CheckMate-067 that were not measured and therefore could not be accounted for in the propensity score adjusted analysis. As a result, the analysis also included a comparison of the nivolumab arms from both trials as an internal validation of the approach. This analysis demonstrated that after weighting there were no differences in PFS and OS outcomes between the nivolumab arm of CheckMate-067 and the nivolumab arm of RELATIVTY-047. Therefore unobserved or unmeasured factors are unlikely to be confounding the adjusted ITC, as if such factors were confounding the analysis this would be expected to present in different performance across the two nivolumab arms.

Finally, there were differences in follow-up duration available from the most recent DBLs of CheckMate-067 and RELATIVITY-047 at the time of analysis. To account for this, data from CheckMate-067 were truncated through artificial censoring to more closely align to the available follow-up time of RELATIVITY-047. Truncation of the CheckMate-067 data emulated the September 2016 DBL of CheckMate-067 and this was chosen as minimum and median follow-up time from this lock most closely aligned with the available follow-up time from RELATIVTY-047 at the time of analysis. Given the time-to-event nature of the efficacy endpoints, the decision to truncate the CheckMate-067 data reduced the likelihood of bias and further strengthens the presented analyses. Safety outcomes were reported cumulatively over the first 28 months of follow-up only. While most safety events are expected to occur early in follow-up, it should be noted that for the data used in this analysis, longer minimum follow-up was available from CheckMate-067 (28 months) compared with RELATIVITY-047 ([redacted]). This may have biased the cumulative safety outcomes reported in favour of nivolumab-relatlimab, although while these differences should be acknowledged, given that the majority of safety events are expected to occur early in follow-up, these differences are not be expected to change the conclusions of the presented analysis.

B.2.9.2.4. Conclusion

Aligning with the NMA, the results of this adjusted ITC suggest PFS (per investigator assessment), and OS are similar between nivolumab-relatlimab and nivolumab + ipilimumab. As per the safety results presented in Section B.2.10.2.2, nivolumab-relatlimab was shown have a more favourable safety profile than nivolumab + ipilimumab, with a lower rate of Grade 3-4 treatment-related toxicities and treatment related toxicities leading to discontinuation.

B.2.10. Adverse reactions

B.2.10.1. RELATIVITY-047 trial

The data presented from the RELATIVITY-047 trial are from the October 2022 data-cut, with a median follow-up duration of [redacted] months (range: [redacted], [redacted] months).[51]

Treatment-related adverse events (TRAEs) were categorised with the use of the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.[58]

B.2.10.1.1. Extent of exposure to trial treatment

At the data-cut of October 2022, the median time to treatment discontinuation was [redacted] months (95% CI: [redacted], [redacted]) in the nivolumab-relatlimab arm, and [redacted] months (95% CI: [redacted], [redacted]) in the nivolumab arm.[51]

Figure 16: Kaplan–Meier plot of time to treatment discontinuation (ITT population)

Key: CI, confidence interval; ITT, intention-to-treat.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.10.1.2. Summary of adverse events

The safety profile of nivolumab-relatlimab was manageable and consistent with the known mechanisms of action of relatlimab and nivolumab. No new safety signals or events were identified when compared with nivolumab.[51]

The nature of AEs was similar between the treatment arms; however, the frequency and severity of all-cause and drug-related AEs, serious AEs, and AEs leading to discontinuation were generally higher in the nivolumab-relatlimab arm compared with the nivolumab arm.[51]

A summary of AEs reported in the RELATIVITY-047 trial is presented in Table 19. A total of [redacted] ([redacted]%) patients in the nivolumab-relatlimab arm and [redacted] ([redacted]%) patients in the nivolumab arm reported an AE of any grade, of which, [redacted] ([redacted]%) in the nivolumab-relatlimab arm and [redacted] ([redacted]%) in the nivolumab arm experienced at least one Grade 3–4 AE.[51]

When assessing TRAEs, these were reported in [redacted] ([redacted]%) patients in the nivolumab-relatlimab arm and [redacted] ([redacted]%) patients in the nivolumab arm.[51]

A total of [redacted] ([redacted]%) patients in the nivolumab-relatlimab arm and [redacted] ([redacted]%) patients in the nivolumab arm experienced AEs that lead to the discontinuation of the trial treatment.[51]

Table 19: Summary of AEs (ITT population)

	Nivolumab-relatlimab (n = 355)		Nivolumab (n = 359)	
	Any Grade	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Any AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TRSAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs leading to discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; ITT, intention-to-treat; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

A summary of the frequently reported TRAEs is presented in Table 20.

The most frequently reported TRAEs in the nivolumab-relatlimab arm compared with the nivolumab arm were pruritus ([redacted]% versus [redacted]%), fatigue ([redacted]% versus [redacted]%), rash ([redacted]% versus [redacted]%) and hypothyroidism ([redacted]% versus [redacted]%).[51]

Table 20: Frequently reported TRAEs (ITT population)

	Nivolumab-relatlimab (n = 355)		Nivolumab (n = 359)	
	Any Grade	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Vitiligo	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]	[redacted]	[redacted]

Key: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ITT, intention-to-treat; TRAE, treatment-related adverse event.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.10.1.3. Immune-mediated adverse events

Table 21 presents the immune-mediated AEs reported by worst CTCAE grade.

The most frequently reported immune-related AEs of any grade in the nivolumab-relatlimab and nivolumab arms were adrenal insufficiency ([redacted]% versus [redacted]%), hypothyroidism and/or thyroiditis ([redacted]% versus [redacted]%) hypothyroidism ([redacted]% versus [redacted]%), and diarrhoea and/or colitis ([redacted]% versus [redacted]%). [redacted] patients experienced Grade 5 immune-mediated AEs.[51]

Table 21: Endocrine and non-endocrine immune-mediated adverse event summary by worst CTCAE grade (ITT population)

	Nivolumab-relatlimab (n = 355)			Nivolumab (n = 359)		
	Any Grade	Grade 3–4	Grade 5	Any Grade	Grade 3–4	Grade 5
Endocrine immune-mediated adverse events						
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism/thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophysitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-endocrine immune-mediated adverse events						
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea/colitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis and renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CTCAE, Common Terminology Criteria for Adverse Events; ITT, intention-to-treat.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.10.1.4. Deaths

Table 22 presents a summary of all deaths in the RELATIVITY-047 trial. Over the median follow-up of [redacted] months, [redacted] ([redacted]%) patients died in the nivolumab-relatlimab arm and [redacted] ([redacted]%) patients died in the nivolumab arm.[51]

[redacted] patients in the nivolumab-relatlimab arm and [redacted] patients in the nivolumab arm experienced treatment-related deaths.[51] The treatment-related cause of death was haemophagocytic lymphohistiocytosis (n = [redacted]), acute oedema of the lung (n = [redacted]), pneumonitis (n = [redacted]) and multi-organ failure (n = [redacted]) in the nivolumab-relatlimab arm, and sepsis and myocarditis (n = [redacted]) and worsening pneumonia (n = [redacted]) in the nivolumab arm.[51]

Table 22: Summary of deaths (ITT population)

	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
Number of patients who died, n (%)	[redacted]	[redacted]
Primary reason for death, n (%)		
Disease progression	[redacted]	[redacted]
Study drug toxicity	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
Number of patients who died within 30 days of last dose, n (%)	[redacted]	[redacted]
Primary reason for death, n (%)		
Disease progression	[redacted]	[redacted]
Study drug toxicity	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]
Number of patients who died within 100 days of last dose, n (%)	[redacted]	[redacted]
Primary reason for death, n (%)		
Disease progression	[redacted]	[redacted]
Study drug toxicity	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Other	[redacted]	[redacted]

Key: ITT, intention-to-treat.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

B.2.10.2. Comparison with key comparators of interest

B.2.10.2.1. Network meta-analysis

As presented in Section B.2.9.1, an NMA was conducted to assess the efficacy and safety for nivolumab-relatlimab versus nivolumab + ipilimumab and pembrolizumab in adults with untreated unresectable or metastatic melanoma. Safety outcomes were less frequently reported across the evidence base than efficacy outcomes; however, NMA was still possible for Grade 3-4 adverse events, Grade 3-4 treatment-related adverse events, discontinuations due to adverse events and discontinuations due to treatment-related adverse events.

All safety analyses were conducted using a fixed-effects model given that there was insufficient evidence available to estimate the between-study heterogeneity required

to run the random effects models. The insufficiency was due to the availability of only a single trial for the key treatment comparisons in the evidence networks.

Compared with nivolumab + ipilimumab, the results of the NMA indicate that treatment with nivolumab-relatlimab was associated with a significantly lower odds of Grade 3–4 AEs (OR [redacted], 95% CrI: [redacted], [redacted]), treatment-related Grade 3–4 AEs (OR [redacted], 95% CI: [redacted], [redacted]), discontinuations due to adverse events (OR [redacted], 95% CrI: [redacted], [redacted]) and discontinuations due to TRAEs (OR [redacted], 95% CrI: [redacted], [redacted]).

When comparing safety profiles for pembrolizumab and nivolumab-relatlimab, treatment-related Grade 3-4 AEs were significantly higher for the dual IO treatment (OR [redacted], 95% CrI: [redacted]). Nivolumab-relatlimab was also associated with a non-significantly higher risk of discontinuations due to adverse events (OR [redacted], 95% CrI: [redacted], [redacted]) and higher risk of discontinuations due to TRAEs (OR [redacted], 95% CrI: [redacted]) compared to pembrolizumab.

B.2.10.2.2. Adjusted indirect treatment comparison

As presented in Section B.2.9.2, an adjusted ITC was performed to assess the efficacy and safety of nivolumab-relatlimab versus nivolumab + ipilimumab using PLD from the RELATIVITY-047 and CheckMate-067 trials. The methods for the ITC and results of the comparison of efficacy outcomes is presented in Section B.2.9.2.

Table 23 presents the safety outcomes for nivolumab-relatlimab and nivolumab + ipilimumab after adjusting for baseline characteristics. Safety outcomes did not change markedly after weighting as compared with outcomes before weighting. After weighting, Grade 3-4 all-cause AEs were higher with nivolumab + ipilimumab ([redacted]%) than with nivolumab-relatlimab ([redacted]%). Similarly, treatment-related adverse events (TRAEs) were higher with nivolumab + ipilimumab (Grade 3-4; [redacted]%, any Grade leading to discontinuation; [redacted]%) than with nivolumab-relatlimab (Grade 3-4; [redacted]%, any Grade leading to discontinuation; [redacted]%).

Table 23: Safety of nivolumab-relatlimab and nivolumab + ipilimumab after weighting (ITT population)

	Nivolumab-relatlimab (n = [redacted])	Nivolumab + ipilimumab (n = [redacted])
All-cause AEs (any grade), %	[redacted]	[redacted]
All-cause AEs (Grade 3-4), %	[redacted]	[redacted]
TRAEs (any grade), %	[redacted]	[redacted]
TRAEs (Grade 3-4), %	[redacted]	[redacted]
TRAEs leading to discontinuation of treatment (any grade), %	[redacted]	[redacted]
Key: AE, adverse events; ITT, intention-to-treat; TRAEs, treatment-emergent adverse events.		

B.2.11. Ongoing studies

The RELATIVITY-047 trial is currently ongoing. The estimated trial completion date is December 2025.[71]

B.2.12. Interpretation of clinical effectiveness and safety evidence

Despite the progress made over the last decade in transforming the treatment pathway for patients with untreated unresectable or metastatic melanoma, additional novel dual checkpoint inhibitors are needed to provide patients with more treatment options, thereby enabling patients to receive a treatment most suitable to them. Nivolumab-relatlimab is a novel dual checkpoint inhibitor that provides comparable efficacy to other dual checkpoint inhibitors (i.e. nivolumab + ipilimumab), whilst exhibiting a more tolerable safety profile. This treatment would enable clinicians to provide a more tailored approach to treatment, depending on factors such as the age of the patient, their performance status, existing comorbidities, and their ability to tolerate potential treatment toxicity.

RELATIVITY-047 provides direct evidence to demonstrate that the FDC of nivolumab-relatlimab offers greater efficacy with a similar safety profile to nivolumab.[51, 58] Over a median follow-up of [redacted] months, nivolumab-relatlimab demonstrated superior PFS compared with nivolumab, with a [redacted]% reduction in risk of progression or death (HR [redacted]; 95% CI: [redacted], [redacted]).[51] Nivolumab-relatlimab also

demonstrated an improvement in OS, though not statistically significant, with a [redacted]% reduction in risk of death (HR [redacted]; 95% CI: [redacted], [redacted]).[51] Nivolumab-relatlimab also had a PFS benefit over nivolumab across the majority of pre-specified subgroups, including patients who had characteristics that were typically associated with a worse prognosis (i.e. high tumour burden and elevated levels of serum LDH).[51] As per the March 2021 database lock, patients reported a stable HRQL (i.e. close to baseline values) which was similar between the two treatment groups.[57]

As there are currently no head-to-head data available for the comparison of nivolumab-relatlimab versus nivolumab + ipilimumab in patients with untreated unresectable or metastatic melanoma, a time-varying NMA and an ITC adjusting for differences in baseline characteristics was conducted to compare OS and PFS. Both the NMA and ITC demonstrated that nivolumab-relatlimab has similar efficacy to nivolumab + ipilimumab in terms of PFS and OS. The time-varying NMA also demonstrated that, when compared to pembrolizumab, nivolumab-relatlimab was shown to provide statistical improvement in PFS from month 3 onwards, and a numerical, but not statistically significant, advantage in OS at all timepoints. Results for the comparison with nivolumab demonstrated that nivolumab-relatlimab was associated with a numerical advantage in PFS, which was statistically significant at Month 3, and OS, aligning with the OS and PFS results presented for the nivolumab-relatlimab and nivolumab comparison in RELATIVITY-047.

Although Grade 3–4 TRAEs were more frequent among patients who received nivolumab-relatlimab compared with nivolumab ([redacted]% versus [redacted]%), no new safety signals associated with nivolumab-relatlimab were identified, and as demonstrated by the NMA and ITC, the safety profile appeared favourable as compared with that reported with nivolumab + ipilimumab.[51]

B.2.12.1. Strengths and limitations of the evidence base

RELATIVITY-047 is the first Phase 3 trial to investigate the dual checkpoint inhibition of LAG-3 and PD-1 in melanoma patients.[51] These results validate the synergistic effect of blocking LAG-3 in combination with PD-1 as a therapeutic strategy for patients with untreated unresectable or metastatic melanoma, and establish LAG-3 as the third immune checkpoint pathway, the inhibition of which shows clinical benefit.

The RELATIVITY-047 trial is a high-quality, randomised trial which adhered to a series of pre-defined steps in order to avoid any potential bias.[65] All patients were centrally randomised using IRT, and the sponsor, participants, investigator, and site staff were blinded to the trial treatment administered. Patients were stratified by pre-specified subgroups at baseline according to LAG-3 expression, PD-L1 status, *BRAF* status and AJCC v8 metastatic stage.[65] RELATIVITY-047 was double-blinded in order to minimise bias, and evaluation of PFS was conducted by a blinded third party, allowing for independent review of the data and even further reduction in the risk of bias.

Of note, RELATIVITY-047 was designed with sufficient power to assess the primary endpoint of PFS per BICR in the ITT population, though not powered to formally evaluate the PFS benefit of nivolumab-relatlimab over nivolumab by biomarker subgroup.[58] The study was not designed to assess OS as a primary endpoint, and with no formal plan of testing OS in the PD-L1<1% subgroup (or any biomarker subgroup), there was not sufficient power to demonstrate a statistically significant effect in OS.

RELATIVTY-047 compares the safety and efficacy of nivolumab-relatlimab with nivolumab. At the point of trial initiation, IO monotherapy was the standard of care for patients with previously untreated metastatic or unresectable melanoma and was therefore chosen as the direct comparator for this trial. As RELATIVITY-047 does not provide a direct comparison to all comparators of interest, indirect comparisons were performed – specifically an NMA to compare nivolumab-relatlimab with nivolumab + ipilimumab, pembrolizumab and nivolumab, and an adjusted ITC to compare nivolumab-relatlimab with nivolumab + ipilimumab, using PLD from RELATIIVTY-047 and CheckMate-067.

While it is positive that the median OS has not yet been reached in the nivolumab-relatlimab arm, from a statistical perspective the survival data are immature. This means extrapolation beyond the trial is required for economic analyses (Section B.3.3).

B.2.12.1.1. Study applicability to clinical practice

The population in RELATIVITY-047 aligns with the population outlined in the decision problem presented in this submission: patients with untreated unresectable or metastatic melanoma. The RELATIVITY-047 trial was conducted at 114 centres across 25 countries worldwide.[56] UK clinicians have confirmed the RELATIVITY-047 trial population was considered to be representative of patients with untreated unresectable or metastatic melanoma within UK clinical practice.[37]

A broad range of patients were enrolled in the RELATIVITY-047 trial in terms of AJCC metastatic stage, melanoma subtype classification, age, race and ECOG performance status at baseline.[47] Baseline patient demographics and disease characteristics were well-balanced between the treatment arms, with the exception of a higher proportion of patients in the nivolumab-relatlimab arm with an AJCC (8th edition) metastasis stage of M1c, a poor prognostic factor relative to lower stage disease.

The primary and secondary efficacy outcomes of PFS and OS, respectively, are well established trial endpoints which are most relevant to patients, carers and healthcare professionals in clinical practice. Treatment options that are clinically active (e.g. ipilimumab, vemurafenib, dabrafenib, trametinib) are increasingly available to patients with unresectable or metastatic melanoma and their use after disease progression on the current study may confound an OS endpoint. PFS is not confounded by post-study treatment therapies and has been demonstrated to correlate with OS in a pooled analysis of immune checkpoint inhibitor trials.[72] In addition, PFS has been recognised as an acceptable regulatory endpoint.

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

An SLR was conducted in January 2022 to identify relevant cost-effectiveness studies relating to treatments for advanced, metastatic melanoma. The SLR was further updated in November 2022.

Full details of the review are available in Appendix G. No cost-effectiveness studies were identified that evaluated nivolumab-relatlimab in previously untreated unresectable or metastatic melanoma. The SLR identified four UK-based studies assessing the cost-effectiveness of immunotherapy interventions for the treatment of advanced, metastatic or unresectable melanoma (Table 24).

Table 24: Summary of published cost-effectiveness analyses

Author, year, country	Objective	Intervention	Comparator	Type of model	Health states	Perspective
Al-Khayat, 2021[73], UK	To assess the impact of implementing treatment coefficient on cost-effectiveness models using mixed cure models.	Pembrolizumab	Ipilimumab	Partitioned-survival analysis model	Progression-free PD Death	UK perspective
Gibson, 2018[74], UK	To explore the impact of incorporating immune-specific health states into economic models of IO therapy. Two variants of the PSM and a Markov model were populated with data from a clinical trial in metastatic melanoma patients	Nivolumab	Dacarbazine	Partitioned-survival model Markov model	Pre-progression Post-progression Death No response Initial immune response Durable immune response	UK national healthcare system perspective
Lee, 2016[75], England	To provide a comparison of overall survival data for ipilimumab, vemurafenib and dacarbazine using data from three trials.	Ipilimumab	Dacarbazine Vemurafenib	N/R	N/R	UK perspective
Meng, 2018[76], UK	To evaluate the cost-effectiveness of nivolumab monotherapy for the treatment of advanced melanoma patients in England.	Nivolumab (*BRAF*-negative patients) Nivolumab (*BRAF* positive patients)	Ipilimumab; dacarbazine (*BRAF* negative) Ipilimumab; vemurafenib; dabrafenib (*BRAF* positive)	Semi-Markov state transition model	Progression-free PD Death	UK perspective

Key: IO, immuno-oncology; PD, progressed disease; PSM, partitioned survival model; QALY, quality adjusted life year

A manual search of the NICE website was conducted in March 2023 to identify HTAs of interest for this appraisal. This hand-searching further identified three appraisals for relevant comparators in advanced and/or metastatic melanoma (TA366: pembrolizumab, TA384: nivolumab, TA400: nivolumab + ipilimumab).[41-43] The features of these HTAs are summarised and compared to the current analysis in Table 26. In addition to the identified HTAs, a health economic model report (HEMR) for advanced and unresectable melanoma published by NICE in 2022 was also identified.[77]

B.3.2. Economic analysis

Due to the lack of existing economic evaluations for nivolumab-relatlimab in previously untreated unresectable or metastatic melanoma, a de novo economic model was built. The model structure and inputs were informed by a review of existing models in this indication, the availability of data from RELATIVITY-047, UK clinical opinion, previous NICE appraisals in melanoma and melanoma guideline development.[36, 37, 42, 77-82]

B.3.2.1. Patient population

[redacted], as described in Section B.1.2.

The economic analysis addresses this patient population directly in line with the RELATIVITY-047 trial population, the expected MHRA label and the final scope issued by NICE.[65]

The modelled baseline characteristics are summarised in Table 25.

Table 25: Baseline patient characteristics

Characteristic	Baseline value	Reference
Age	[redacted]	RELATIVITY-047[65]
% male	[redacted]	RELATIVITY-047[65]
Weight	[redacted]	RELATIVITY-047[65]
BSA	[redacted]	RELATIVITY-047[65]
Indication	[redacted]	RELATIVITY-047[65]

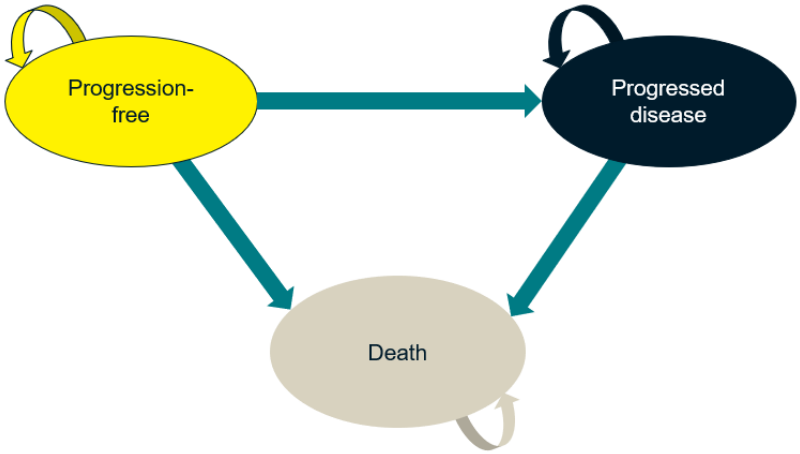
Key: BSA, body surface area; SD, standard deviation

B.3.2.2. Model structure

The economic model developed to assess the cost-effectiveness of nivolumab-relatlimab follows a standard three-state partitioned survival modelling approach, using the area under the curve to define patient movement between states. Patients are assigned to one of three mutually exclusive health states: progression-free (PF), progressed-disease (PD) or dead in the model based on PFS and OS curves (see Figure 17 for model schematic). Patients enter the model in the 'progression-free' state, receiving nivolumab-relatlimab or a comparator treatment. Patients may remain progression-free, they may progress, or they may die. Patients whose disease has progressed can remain alive with PD or die. Death is an absorbing state. To accurately capture drug administration and acquisition costs, alive states are further separated into on- and off-treatment (where treatment refers to 1L treatment received). Patients may discontinue 1L treatment before or after progression, meaning that they enter either the pre-progression off-treatment or post-progression off-treatment states. In the base case, a limit is built into TTD that does not allow it to exceed PFS and treatment stopping rules are also applied (further details provided in Section B.3.3.5).

Health state occupancy was evaluated at 1-month-cycle intervals (in line with the NICE Melanoma HEMR) over the course of the modelled time horizon (40 years, representing a lifetime) to maximise precision in treatment cost assignment and estimates of progression.[77] The cumulative survival probabilities for PFS and OS were used to estimate the number of patients occupying each health state. The model has also been developed so that PFS cannot exceed OS to prevent clinically implausible results.

Figure 17: Model structure schematic



The partitioned survival modelling approach is widely employed in cost-effectiveness assessments of oncological interventions, and there is precedent that this form of modelling has been reviewed and accepted in many previous NICE appraisals. In addition, this approach is consistent with the prior models submitted to NICE for treatments for melanoma (TA319, TA366, TA396, TA410, TA414, TA562) and the NICE Melanoma HEMR.[42, 77-82] Furthermore, PFS and OS data are available for all treatments of interest from their respective pivotal trials as primary or secondary outcomes. Therefore, this modelling approach aligns with the use of the most robust available data for both nivolumab-relatlimab and comparators. Age-adjusted all-cause background mortality is applied; the adjustment for background mortality was considered necessary because of the extended time horizon of the model. The background mortality risk in each time cycle was compared with the corresponding risk of death predicted by the selected extrapolation, and the model applies the higher of the two risk values when calculating the survival in the next interval. In addition to background mortality, half-cycle correction is applied in the base case.

Use of immunotherapies in advanced melanoma leads to long-term survivorship for a subset of patients. For these patients, the hazard of death increases due to ageing, which leads to a natural waning of treatment effects (further details provided in Section B.3.3.6).

Table 26 summarises key features of the economic analysis, alongside corresponding features of completed NICE appraisals in melanoma.

Table 26: Features of the economic analysis

Factor	Previous evaluations			Current evaluation	
	TA400[41]	TA384[43]	TA366[42]	Chosen approach	Justification
Indication	Advanced melanoma	Advanced (unresectable or metastatic) melanoma	Advanced melanoma not previously treated with ipilimumab	[redacted]	Aligned to anticipated indication
Intervention	Nivolumab + ipilimumab	Nivolumab	Pembrolizumab	Nivolumab-relatlimab	N/A
Model structure	Markov state-transition	Markov state-transition	Partitioned survival model	Partitioned survival model	Standard approach consistent with previous NICE TAs in oncology (including melanoma) that require indirect comparisons. Uses key endpoints from RELATIVITY-047 (OS, PFS). Validated by health economic experts[37]
Discount rate	3.5% per annum (for costs, LYs and QALYs)	3.5% per annum (for costs, LYs and QALYs)	3.5% per annum (for costs, LYs and QALYs)	3.5% per annum (for costs, LYs and QALYs)	Consistent with the NICE reference case[83]
Time horizon	Lifetime (40 years)	Lifetime (40 years)	Lifetime (30 years)	Lifetime (40 years)	Consistent with the NICE reference case[83]
Cycle length	1 week	1 week	1 week	1 month	In line with NICE Melanoma HEMR[77]
Stopping rule	Applied to all treatment arms at 2 years. No other relevant stopping rules.	Applied to nivolumab at 2 years. No other relevant stopping rules.	Modelled treatment duration using progression-free survival	Applied to all treatment arms at 2 years	In line with NICE TA400, TA384, NICE Melanoma HEMR and UK clinical expert opinion[37, 41, 77]

Factor	Previous evaluations			Current evaluation	
	TA400[41]	TA384[43]	TA366[42]	Chosen approach	Justification
Treatment waning effect?	Not explicitly discussed; company's base-case assumed equal post-progression survival.	Not explicitly discussed; company's base-case assumed same survival after three years	Not explicitly discussed; company's base-case assumed same survival after one year	Natural waning of relative treatment effect	Hazard function of treatment arms intersect with general population hazards; this leads to a natural loss of relative treatment effects as long-term hazards then increase, thus accounting for a waning effect. This assumption is strongly supported by long-term data from CheckMate-067 which show observed hazards intersecting with general population hazards[84, 85]
Subsequent treatment	Four subsequent treatments considered: pembrolizumab, ipilimumab, dabrafenib and vemurafenib	Four subsequent treatments considered: pembrolizumab, ipilimumab, dabrafenib and vemurafenib	Once patients progressed, no further subsequent active therapies were administered and patients only received palliative care	Subsequent treatment included in the base case. Determined by 1L treatment administered and *BRAF* status	In line with NICE Melanoma HEMR and UK clinical expert opinion[37, 41, 77]
Source of utilities	EQ-5D from CheckMate-067	EQ-5D from CheckMate-066	EQ-5D from KEYNOTE-006	EQ-5D from RELATIVITY-047	Consistent with the NICE reference case.[83] Alternative utility estimates explored in scenario analyses
Source of costs	NHS reference costs, PSSRU, BNF, MIMS, eMIT, published literature			NHS reference Costs, PSSRU, BNF, MIMS, eMIT, Published literature	Standard UK reference costs. Consistent with previous appraisals and the NICE reference case for the cost perspective[83]
Source of resource use	MELODY trial	MELODY trial	MELODY trial	NICE TA400	In line with NICE TA400, TA384, NICE Melanoma HEMR and UK clinical expert opinion[37, 41, 77]

Key: BNF, British National Formulary; eMIT, electronic Market Information Tool; HEMR, health economic modelling report; LY, life year; N/A, not applicable; MIMS, Monthly Index of Medical Specialities; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; TA, technology appraisal.

B.3.2.3. Intervention technology and comparators

The intervention technology is nivolumab-relatlimab, with the following treatments as comparators: nivolumab, nivolumab + ipilimumab, and pembrolizumab. Selected comparators were in alignment with the NICE scope and also validated with clinical experts following an advisory board.[37]

For the intervention, two 320 mg vials (240 mg of nivolumab and 80 mg of relatlimab) of the FDC are given intravenously every 4 weeks (Q4W). In RELATIVITY-047, patients continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, or end of the trial; as such, there was no stopping rule for nivolumab-relatlimab.[65] However, in UK clinical practice, clinicians have the option to discontinue IO treatment for melanoma at 2 years. Thus, it is assumed that nivolumab-relatlimab will be administered until disease progression or a maximum treatment duration of 2 years, in line with UK clinical expert opinion.[37] This is consistent with the duration of treatment used for the immunotherapies, nivolumab and pembrolizumab.

Table 27 summarises dosing regimens of the modelled comparators.

Table 27: Summary of comparator regimens

Treatment	Dosage	Treatment rules	Justification
Nivolumab	Nivolumab 480 mg IV Q4W	Duration of nivolumab treatment = 2 years, in line with UK clinical expert opinion[37]	In line with nivolumab UK SmPC, RELATIVITY-047, and NICE Melanoma HEMR[44, 65, 77]
Nivolumab-ipilimumab	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W for four cycles followed by nivolumab 480 mg IV Q4W	Duration of nivolumab treatment = 2 years, in line with UK clinical expert opinion[37]	In line with NICE Melanoma HEMR and UK SmPC[44, 46, 77]
Pembrolizumab	400 mg Q6W	Duration of pembrolizumab treatment = 2 years, as per pivotal trial (KEYNOTE-006) and in line with UK clinical expert opinion[37]	In line with pembrolizumab UK SmPC and NICE Melanoma HEMR[45, 77]

Key: HEMR, health economic modelling report; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; SmPC, summary of product characteristics.

Variation in treatment stopping rules for intervention and comparator treatments was explored in a scenario analysis (Section B.3.10.2). Further details of this are provided in Section B.3.3.5.

B.3.3. Clinical parameters and variables

B.3.3.1. Overview of clinical outcomes and approach to data analysis

The primary source of clinical data for the economic model is the pivotal study for nivolumab-relatlimab; the RELATIVITY-047 trial, which is an ongoing, Phase II/III, double-blind trial. A detailed summary of methodology and patient flow in the RELATIVITY-047 trial is provided in Section B.2.3 and Section B.2.4.3, respectively.

RELATIVITY-047 data are pivotal in informing assumptions in the economic model generally, and their clinical parameters and variables specifically (Table 28).

Table 28: Clinical evidence from RELATIVITY-047 used in the cost-effectiveness analysis

Clinical evidence	Brief description	Use in the model
OS	OS was defined as the time between the date of randomisation and the date of death due to any cause.	Defines health state membership
PFS	PFS was defined as the time between the date of randomisation and the first date of documented progression, or death due to any cause, whichever occurred first.	Defines health state membership
TTD	TTD was defined as the time from the date of randomisation until the date of treatment discontinuation	Used to estimate the duration and intensity of treatment for cost calculations
AE	The assessment of safety was based on frequency of deaths, AEs, SAEs, AEs leading to discontinuation of study drug, and abnormalities in specific clinical laboratory assessments. Analyses were conducted using the 30-day and/or 100-day safety window from day of last dose received. AEs were coded using the MedDRA version 23.1. AEs were graded for severity according to the NCI CTCAE version 5.0.	Modelling duration and incidence of adverse events
HRQL	Summary of measures of EQ-5D-3L VAS and utility index scores	EQ-5D-3L utility index scores were used to estimate health-state utility values
Key: AE, adverse event; HRQL, health-related quality of life; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event; TTD, time to treatment discontinuation.		

Parametric survival analyses of RELATIVITY-047 OS, PFS and TTD data inform health state occupancy in each cycle of the nivolumab-relatlimab and nivolumab arms of the economic model. CheckMate-067 and KEYNOTE-006 are used to inform relative treatment effect estimates for nivolumab + ipilimumab and pembrolizumab, respectively, for the comparison versus nivolumab-relatlimab, as described in Section B.2.9.1.

The remainder of Section B.3.3 describes the methodology, data and results of parametric survival analyses to estimate and extrapolate OS, PFS and TTD data over a lifetime horizon, described in respective sub-sections. Each endpoint-defined subsection also describes the use of NMA results and other assumptions to populate clinical effectiveness parameters for nivolumab + ipilimumab and pembrolizumab model arms.

B.3.3.2. Approach to time-to-event analysis

Key efficacy outcomes (OS, PFS, TTD) for nivolumab-relatlimab and nivolumab were modelled using PLD from RELATIVITY-047 (data cut-off October 2022). The median duration of follow-up was approximately [redacted] months in the nivolumab-relatlimab arm and [redacted] months in the nivolumab arm. In line with the NICE reference case, to assess the cost-effectiveness of nivolumab-relatlimab over a lifetime horizon it was necessary to extrapolate the PLD beyond the trial period. Methods used to extrapolate OS, PFS and TTD followed guidance outlined in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[86, 87]

For nivolumab and nivolumab-relatlimab, parametric models used in the base-case analysis were assessed systematically for each endpoint, based on the following approach:

- Following NICE DSU TSD 14, standard parametric models were fitted to the observed data from RELATIVITY-047 and assessed for suitability considering[86, 87]:
  - Assessment of proportional hazards
  - Visual fit to the observed KM data within the trial period for RELATIVITY-047
  - Assessment of the underlying hazard functions
  - Statistical goodness of fit indicated by Akaike information criterion (AIC) and Bayesian information criterion (BIC) values

- Additional flexible piecewise (KM plus parametric) and spline models were explored where necessary, in accordance with NICE DSU TSD 21, and assessed for suitability based on the same process[86, 87]
- Clinical validation of extrapolated models was based on opinions of UK clinical experts derived from an advisory board.[37] Extrapolations were also compared against relevant long-term evidence of immunotherapies (see Section B.3.3.2.1 for further details)

In the absence of head-to-head data for the comparisons of nivolumab-relatlimab versus either nivolumab + ipilimumab or pembrolizumab, a NMA was performed. Details of the OS and PFS NMA model selection process are detailed in Section B.2.9.1. Near-complete TTD data for nivolumab + ipilimumab and pembrolizumab for the indicated patients were obtained from the most appropriate sources. Clinical validation of extrapolated models was based on opinions of UK clinical experts derived from an advisory board[37] and by comparison with external evidence. Alternative clinically plausible models were tested in scenario analyses.

Table 29 and Table 30 summarise the OS, PFS and TTD base case and scenarios for each of the comparisons. Full details are provided in Section B.3.3.3 for OS, Section B.3.3.4 for PFS, and Section B.3.3.5 for TTD.

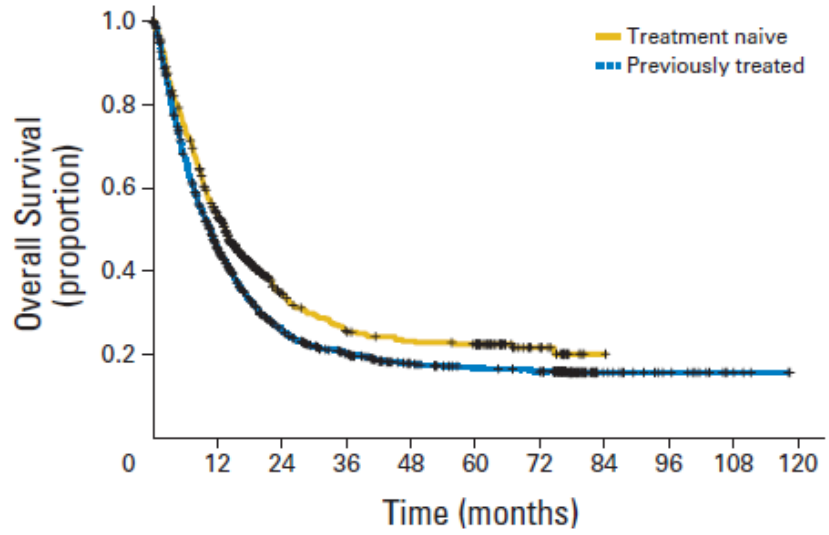
B.3.3.2.1. Long-term melanoma survivorship with immunotherapies

A key component of this evaluation is the long-term extrapolation of clinical outcomes (OS and PFS). For immunotherapies (ipilimumab, nivolumab, nivolumab + ipilimumab and pembrolizumab), there is strong long-term evidence from several sources that demonstrate a clear and sustained plateau when used in the treatment of advanced melanoma.[35, 84, 85, 88-90]

The longest available follow-up is for ipilimumab (10-year OS follow-up based on pooled studies).[88] Data from CheckMate-067 have also been published for OS and PFS with a minimum follow-up of 7.5 years; this includes ipilimumab, nivolumab, and nivolumab + ipilimumab.[35, 90] Evidence from these sources is presented in Figure 18 and Figure 19. The 10-year follow-up shows a clear persistent plateau, with slightly increased rates for treatment-naïve patients. This is reflected in the ipilimumab arm

of CheckMate-067, which also shows that a similar plateau (albeit at notably higher levels) is observed for both nivolumab, and nivolumab + ipilimumab.

Figure 18: Long-term survival following ipilimumab treatment

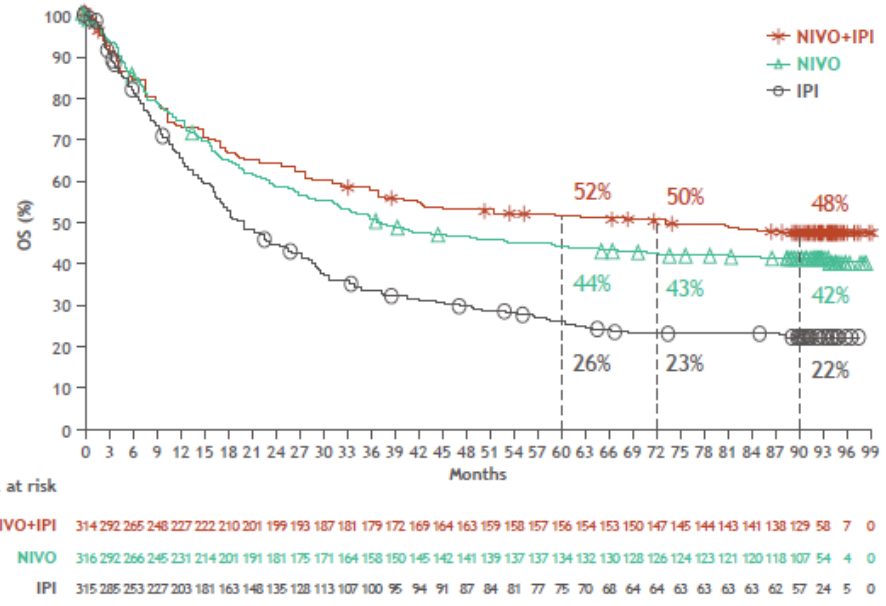


No. at risk											
Treatment naive	604	301	106	74	64	60	18	1	0	0	0
Previously treated	1,257	538	264	180	128	110	102	25	15	5	0

Figure 19: Long-term OS and PFS from CheckMate-067

(A) OS

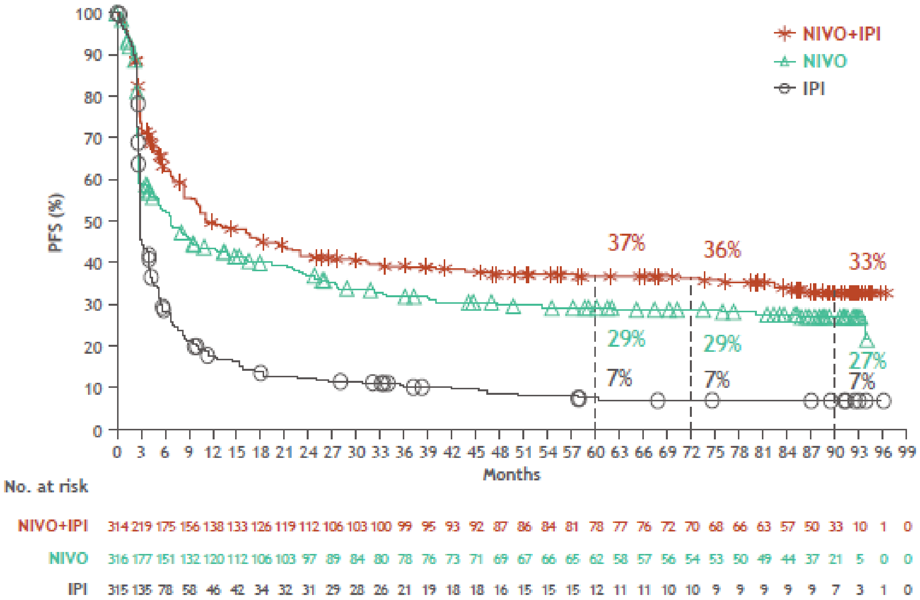
	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.53 (0.44-0.65)	0.63 (0.52-0.77)	-
HR (95% CI) vs NIVO[a]	0.84 (0.68-1.04)	-	-



No. at risk																														
NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	158	157	156	154	153	150	147	145	144	143	141	138	129	58	7	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	137	134	132	130	128	126	124	123	121	120	118	107	54	4	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	75	70	68	64	64	63	63	63	63	62	57	24	5	0

(B) PFS

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median, mo (95% CI)	11.5 (8.9-20.0)	6.9 (5.1-10.2)	2.9 (2.8-3.1)
HR (95% CI) vs IPI	0.42 (0.35-0.51)	0.53 (0.44-0.64)	-
HR (95% CI) vs NIVO[a]	0.79 (0.65-0.97)	-	-



Key: CI, confidence interval; IPI, ipilimumab; NIVO, nivolumab; NIVO+IPI, nivolumab + ipilimumab, OS, overall survival; PFS, progression-free survival

Further analysis of long-term CheckMate-067 data demonstrates a long-term decrease in the hazard of mortality for all three treatments, with those for nivolumab + ipilimumab reaching general population mortality at approximately 5 years, as demonstrated in Figure 20.[84] Similar trends are also observed for PFS (Figure 21; internal analysis). Of note, both Figures present observed hazards; hence the intersection with general population mortality occurs within the trial follow-up. This convincingly demonstrates that long-term survival similar to that of the general population occurs for patients with advanced melanoma who are treated with immunotherapies.

Figure 20: Long-term observed hazards of mortality from CheckMate-067

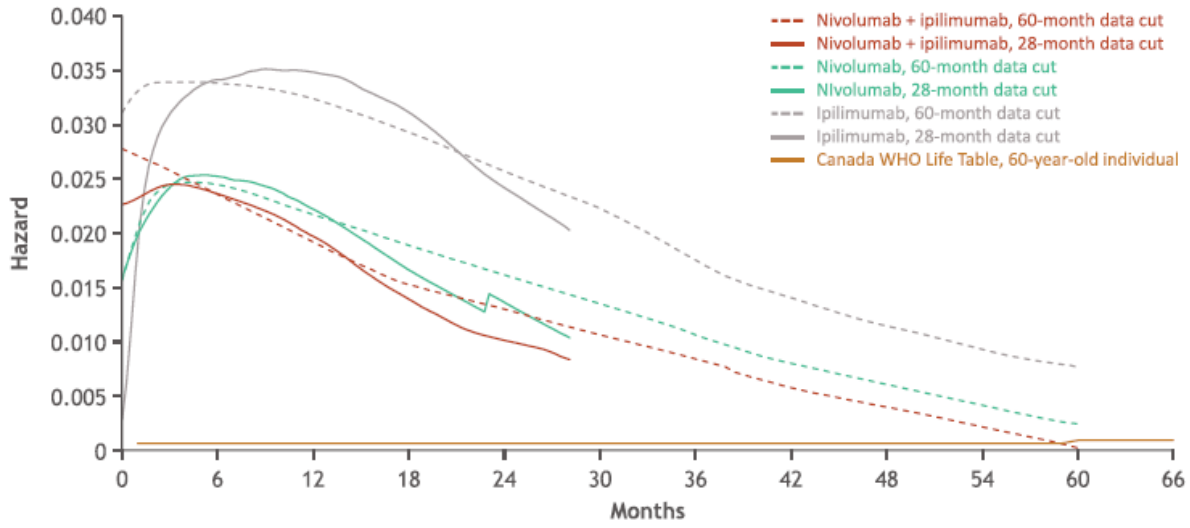
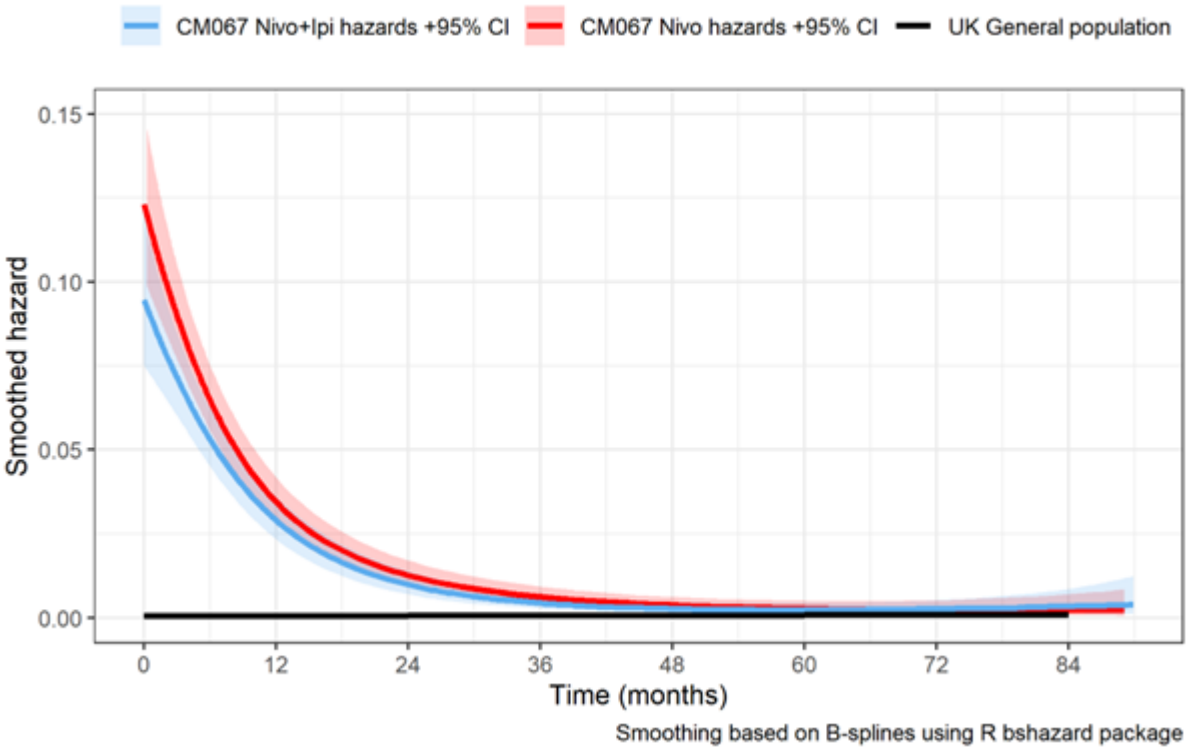


Figure 21: Long-term observed hazards of progression/mortality from CheckMate-067



Key: CI, confidence interval; Nivo, nivolumab; Nivo+Ipi, nivolumab + ipilimumab

Whilst of shorter duration, 5-year follow-up of KEYNOTE-006 (pembrolizumab, ipilimumab) and CheckMate-066 (nivolumab) also demonstrate plateaus in both OS and PFS, consistent with the concept of long-term survivorship in advanced melanoma following treatment with immunotherapy.[89, 91]

Hence, a long-term plateau in both OS and PFS is expected for both treatment arms of RELATIVITY-047. Whilst a novel investigational product, nivolumab-relatlimab includes nivolumab, and as such, clinical expert position was that a similar long-term plateau can also be expected.[37] In addition, the similarity of outcomes between nivolumab-relatlimab and nivolumab + ipilimumab is demonstrated in Section B.2.9. Because of this, the long-term plateau for nivolumab-relatlimab is expected to be of a similar magnitude to that observed for nivolumab + ipilimumab.

The existence of a subset of patients with long-term survival suggests that survival models incorporating this heterogeneity may be appropriate for extrapolation. This has been examined in a number of case-studies of advanced melanoma, [85, 92-95] as discussed in more detail in Section B.3.3.3.1.1. Whilst this suggests a potential role for mixture-cure models (given the existence of long-term survivorship for both OS and PFS), these were not considered due to the immaturity of RELATIVITY-047.

Table 29: Summary of OS and PFS base-case assumptions and scenarios

Treatment arm	OS (Section B.3.3.3)	Justification (OS)	PFS (Section B.3.3.4)	Justification (PFS)	Scenarios (OS/PFS)
Nivolumab-relatlimab	Gompertz	Good visual fit to the observed RELATIVITY-047 KM, smoothed hazards and statistical fit. Only model to capture the expected 'plateauing effect' for nivolumab and nivolumab-relatlimab OS, supported by CheckMate-067 long term data, NMA, ITC and clinical expert opinion at an advisory board.	Piecewise model: KM (first 3 months) + Gompertz	Good visual fit to the observed RELATIVITY-047 KM and smoothed hazards. Piecewise approach justified by strong evidence for change in hazards at 3-month in both treatment arms based on visual assessment of observed KM and PFS hazards, further supported by Chow structural change test. Only model to appropriately capture the expected 'plateauing effect' for nivolumab and nivolumab-relatlimab PFS, supported by CheckMate-067 long-term data, NMA, ITC and clinical expert opinion at an advisory board.	**OS:** Generalised gamma (good visual fit to the observed RELATIVITY-047 KM, smoothed hazards and statistical fit) **PFS:** Spline 1 knot – odds (good visual fit to the PFS KM, smoothed hazards, statistical fit and long-term extrapolation on each arm)
Nivolumab	Gompertz		Piecewise model: KM (first 3 months) + Gompertz		
Nivolumab + ipilimumab	Nivolumab + ipilimumab time varying HRs applied to nivolumab reference curve (derived from the NMA detailed in Section B.2.9.1)	Best-fitting model (second order FP) provides a plausible fit to the observed OS data in CheckMate-067. OS curve produced captures expected long-term survivorship and aligns with clinical expert opinion on the expected plateau in OS.	Nivolumab + ipilimumab time varying HRs applied to nivolumab reference curve (derived from the NMA detailed in Section B.2.9.1)	Best-fitting model (second order FP) provides a plausible fit to the observed PFS data in CheckMate-067. PFS curve produced captures expected long-term PFS and aligns with clinical expert opinion on the expected plateau in PFS.	N/A
Pembrolizumab	Pembrolizumab time varying HRs applied to nivolumab reference curve (derived from the NMA detailed in Section B.2.9.1)	Best-fitting model (second order FP) provides a plausible fit to the observed OS data in KEYNOTE-006.	Pembrolizumab time varying HRs applied to nivolumab reference curve (derived from the NMA detailed in Section B.2.9.1)	Best-fitting model (second order FP) provides a plausible fit to the observed OS data in KEYNOTE-006.	**OS and PFS:** Pembrolizumab PFS set equal to nivolumab reference curve (inferred from clinical expert comments at an advisory board (Section B.2.9.1.3)

Key: FP, fractional polynomial; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

Table 30: Summary of TTD base-case assumptions and scenarios

Treatment arm	Base case*	Justification	Scenarios	Scenarios (all treatment arms)
Nivolumab-relatlimab	Weibull	Good visual fit to the observed RELATIVITY-047 KM, smoothed hazards and statistical fit.	Gamma	The following scenarios were explored on each treatment arm simultaneously: TTD uncapped by PFS (i.e. TTD can exceed PFS) Apply stopping rule at 5 years (note: base case is 2-year stopping rule) 10% of patients continue treatment beyond 2 years
Nivolumab	Weibull	Good visual fit to the observed RELATIVITY-047 KM, smoothed hazards and statistical fit. Aligns closely with long-term data from CheckMate-067.	CheckMate-067 KM data ([redacted]% complete)	
Nivolumab + ipilimumab	CheckMate-067 KM data	KM data are [redacted]% complete.	N/A	
Pembrolizumab	Pembrolizumab TTD set equal to nivolumab reference curve	TTD data not readily available from KEYNOTE-006. Clinical experts advised that the TTD for pembrolizumab and nivolumab is highly similar in clinical practice. Ensures consistent use of trial data for all comparisons.	SACT KM data (98% complete)	

Key: KM, Kaplan–Meier; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy; TTD, time to treatment discontinuation.

Notes: *A 2-year treatment stopping rule and limit to which TTD cannot exceed PFS is applied in the model base case as detailed in Section B.3.2.3

B.3.3.3. Overall survival

B.3.3.3.1. Nivolumab-relatlimab and nivolumab

Figure 22 shows the OS KM data for all patients in RELATIVITY-047 and the corresponding underlying number at risk over time by trial arm. The KM plot shows a similar trend for OS for both treatment arms, with a lower risk of death in the nivolumab-relatlimab arm and an early and sustained separation in curves (OS benefit of nivolumab-relatlimab at 1 year [redacted]% [redacted]% versus [redacted]%], at 2 years [redacted]% [redacted]% versus [redacted]%], at 3 years [redacted]% [redacted]% versus [redacted]%], at 4 years [redacted]% [redacted]% versus [redacted]%]). The number of events and level of maturity of OS is presented in Table 31.

Figure 22: RELATIVITY-047 overall survival, Kaplan–Meier curves

Key: CI, confidence interval; OS, overall survival
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

Table 31: Number of events and level of maturity of OS in RELATIVITY-047

Endpoint	Outcome	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
OS	Number of events	[redacted]	[redacted]
	Maturity (%)	[redacted]	[redacted]
Key: OS, overall survival			

B.3.3.3.1.1. Standard parametric models

As the NICE DSU TSD 14 states, when PLD are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach. Nonetheless, the proportional hazards assumption was tested for completeness.[86] Details of the Schoenfeld residuals and log-cumulative hazard plots are provided in Appendix O, which confirm that it is appropriate to extrapolate OS outcomes based on individually fitted curves for each trial arm, noting that this approach will include dependent models as a special case, and is also consistent with the use of time-varying HRs in the NMA (Section B.2.9).

Due to the immaturity of the data, the NICE DSU TSD 14 guidance was followed to explore parametric model (exponential, Weibull, gamma, log-normal, log-logistic, Gompertz and generalised gamma) extrapolations to capture OS over a lifetime horizon.[86] An overlay of the independent one-piece parametric models and observed KM data from RELATIVITY-047 are shown in Figure 23 and Figure 25 for nivolumab and nivolumab-relatlimab respectively. CheckMate-067 OS data have also been included in both Figures to inform the validity of long-term survival estimates (given the similarity in OS for nivolumab-relatlimab and nivolumab + ipilimumab demonstrated in Section B.2.9).

Smoothed hazards for nivolumab and nivolumab-relatlimab are shown in Figure 24 and Figure 26, respectively. The AIC and BIC statistics are provided in Table 32.

Figure 23: OS independent one-piece parametric survival curves for nivolumab

Figure 24: OS independent one-piece hazard plots for nivolumab

Figure 25: OS independent one-piece parametric survival curves for nivolumab-relatlimab

Figure 26: OS independent one-piece hazard plots for nivolumab-relatlimab

Table 32: Fit statistics of OS standard parametric extrapolation

Treatment	Nivolumab-relatlimab		Nivolumab	
Extrapolation	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

Based on assessment of the single-fitted curves against the observed data from RELATIVITY-047 and longer-term study CheckMate-067 (minimum 7.5-year follow-up), it is evident that most parametric survival models either provided poor fit to the observed data, or lack clinical plausibility, and are therefore not appropriate for decision-making.[35, 90]

For both treatment arms, the exponential, Weibull and gamma models all exhibit a poor visual fit to the KM and do not capture the trend in the smoothed hazard. The log-logistic and log-normal models provide a better visual fit to the KM (specifically to nivolumab) but still overestimate the hazard of death for both treatment arms.

Of all the models fitted, for both the nivolumab and nivolumab-relatlimab arms, the generalised gamma and Gompertz models exhibit a good visual and statistical fit to the observed RELATIVITY-047 KM data and smoothed hazards. However, in both treatment arms, the Gompertz model provides a better visual fit to the smoothed hazard and is the only curve that presents a plateau in OS, with hazards reaching the general population hazards after 100 to 120 months (after which time any modelled hazards increase due to ageing).

Results of the adjusted ITC presented in Section B.2.9.2 demonstrate that the OS for nivolumab-relatlimab (from RELATIVITY-047) is similar to that observed for nivolumab + ipilimumab (from CheckMate-067; statistically non-significant HR of [redacted], 95% CI [redacted] to [redacted]). This result is supported by the NMA (e.g. statistically non-significant HRs of [redacted] from Months [redacted] to [redacted]). Similarly the adjusted ITC

demonstrates comparability across the nivolumab arms of both trials (statistically non-significant HR of [redacted], 95% CI [redacted] to [redacted]). Therefore, long-term data from CheckMate-067 was used to inform the plausibility of the long-term extrapolations from RELATIVITY-047. This comparison demonstrated that all of the standard parametric models underestimate long-term survival for both treatments when compared with long-term CheckMate-067 data, with the Gompertz displaying the closest alignment, followed by the generalised gamma, which underpredicts CheckMate-067 data to a higher degree than Gompertz (Appendix O).

- CheckMate-067 demonstrates that for patients treated with nivolumab, the 7.5-year survival rate is 42% (Figure 19).[35, 90] Apart from the Gompertz model ([redacted]%), all survival models predicted 7.5-year survival rates ≥10% lower than this (landmark OS probabilities are detailed in Appendix O).

- For patients treated with nivolumab + ipilimumab, the 7.5-year survival rate is 48% in CheckMate-067 (Figure 19).[35, 90] Most survival models predicted 7.5-year survival rates for patients treated with nivolumab-relatlimab ≥10% lower than this, with the highest survival rate being produced by the Gompertz model ([redacted]%) (landmark OS probabilities are detailed in Appendix O).

Consistent with NICE TSD guidance for validating extrapolations, both clinical input and learnings from the literature were also explored.[86, 87] These are discussed in turn.

The PFS and OS profiles from the pivotal trials for each treatment of interest were shown to UK clinical experts at an advisory board[37], and the proportion of patients who are anticipated to have progressed, or died at 10 and 20 years was considered. For all treatments there was general consensus that if a patient has not died or progressed at 3–5 years, then (as demonstrated by the KM data) patients were unlikely to progress or die from melanoma, and would die from other causes. This is further demonstrated by long-term data, which demonstrate a rapidly decreasing hazard of both mortality and disease progression over time (Figure 20 and Figure 21), and reflects the clinical approach to discontinue surveillance after 5 years, as observed hazards have intersected general population hazards by this time-point. The experts agreed there was no suggestion in the RELATIVITY-047 data that

nivolumab-relatlimab would not provide similar long-term PFS/OS profiles to nivolumab + ipilimumab, given that both contain nivolumab within the combination.

Paly et al (2022) demonstrated with CheckMate-067 data that standard parametric models (including the “best fitting” Gompertz model) underestimate longer-term survival when using the earlier data cuts, and that survival models incorporating survival heterogeneity (here, due to the subset of long-term survivors) have shown greater accuracy.[84] This result was consistent with previous case studies in treatment-naïve advanced melanoma examining mixture cure models to reflect the heterogeneity in the population (with a proportion of patients achieving long-term survival).[85, 92-95] As explained above, it therefore should be considered conservative by using Gompertz to model OS, which is further evidenced when comparing estimates by the standard parametric models used in this submission to the longer-term landmark OS values and the estimated proportion of long-term survivors based on mixture cure modelling from CheckMate-067 (Mohr et al from ESMO).[85] For example, the estimated proportions of long-term survivors from the best fitting models were 45% (ranges of estimated proportions across models: 38-46%) for nivolumab and 54% (range across models: 49-54%) for nivolumab + ipilimumab. Therefore, the use of Gompertz to model OS in this submission may be predicting conservative estimates of long-term survival in this disease setting.

To conclude, in both treatment arms, the ‘plateauing effect’ presented by the Gompertz model, with long-term decreasing hazards, captures an expected long-term survivorship of these patients (as demonstrated in Section B.3.3.2.1, and based on clinical expectation for patients receiving a PD-L1 inhibitor in this indication[37]), albeit the true magnitude of long-term survivorship is likely to be under-estimated when compared with long-term data from CheckMate-067.

B.3.3.3.1.2. Spline models

Alternative survival models were explored in parallel to standard parametric models, with the aim to improve the validity of OS extrapolations for nivolumab-relatlimab and nivolumab. Consistent with guidance published in NICE DSU TSD 14 and 21, independent spline models were analysed.[86, 87] Full details regarding the construction and exploration of spline models for OS are provided in Appendix O.

In both the nivolumab and nivolumab-relatlimab arms, all spline models demonstrate a reasonable fit to their respective KM curves and smoothed hazards. However, they do not demonstrate any improvement over the generalised gamma model, yet carry added complexity. Similar to all standard parametric models explored, no spline models exhibited the expected 'plateauing effect' for nivolumab or nivolumab-relatlimab OS; this effect was only captured by the Gompertz model.

The generalised gamma presents an alternative to the Gompertz, with more conservative estimates (i.e. does not present the expected plateau), but still demonstrates survival more in line with CheckMate-067 than the other models considered. Hence, the generalised gamma model was explored in scenario analyses (Section B.3.10.2).

B.3.3.3.2. Nivolumab + ipilimumab

As detailed in Section B.2.9.1, an NMA was conducted to estimate the relative treatment effect of nivolumab-relatlimab versus other immunotherapies (including nivolumab + ipilimumab and pembrolizumab). As the proportional hazards assumption did not hold for all the studies in the NMA, fractional polynomial NMAs (which provide time-varying treatment effects) were used.[67, 68]

The model selection process concluded that the best-fitting model was the second-order fractional polynomial (P1=1, P2=-1, scale and 2nd shape) (Section B.2.9.1). Trial-specific KM curves overlaid with the modelled survival curves from the best fitting distribution are available in Appendix O. It is evident that the nivolumab + ipilimumab fractional polynomial curve presents internal validity, providing a plausible fit to the observed OS data in CheckMate-067.

Cumulative survival over time was estimated by applying the nivolumab + ipilimumab HRs generated from the NMA to a reference modelled survival for nivolumab (Gompertz model fit to the nivolumab KM, as detailed in Section B.3.3.3.1.1). The resulting nivolumab + ipilimumab curve captures the expected long-term survivorship and aligns with clinical opinion on the expected plateau in OS (Figure 27).[37]

B.3.3.3.3. Pembrolizumab

The approach used for pembrolizumab was the same as that taken for nivolumab + ipilimumab (see Section B.3.3.3.2).

As mentioned in Section B.2.9.1.3, UK clinical experts expressed concerns around the usefulness of the KEYNOTE-006 trial for the comparison with pembrolizumab in the NMA due to differences in patient characteristics (particularly the inclusion of a subgroup of patients with prior treatment).[37] In addition, there was a general consensus from UK-based clinicians that pembrolizumab and nivolumab monotherapies have a similar efficacy and safety profile.[37] This was explored in a scenario analysis that assumed equal clinical outcomes between pembrolizumab and nivolumab (Section B.3.10.2).

B.3.3.3.4. Summary of base-case selections

The most appropriate and clinically plausible models for OS, given the available external evidence, are used in the base case analysis, as summarised in Table 29 and illustrated in Figure 27.

- For nivolumab-relatlimab and nivolumab, the Gompertz model was used. This provides a plausible fit to the observed data, a good statistical fit, and a clinically plausible long-term extrapolation, albeit with likely under-estimation of the absolute rates of long-term survivors.
- For nivolumab + ipilimumab and pembrolizumab, OS was estimated based on relative treatment effects from the NMA, which are represented by time-varying HRs relative to nivolumab

In base case model selection, clinical plausibility was assessed through consistency with longer-term data from related sources (where appropriate) which as validated by UK clinical experts in an advisory board.[37] All curves selected captured expected long-term survivorship of the indicated patients and were aligned with clinical expectation. Alternative assumptions were tested in scenario analyses (Section B.3.10.2), although these failed to reflect anticipated long-term survivorship. OS projections are bound by age-matched general population predictions, sourced from the latest available Office for National Statistics (ONS) Life Tables.[96]

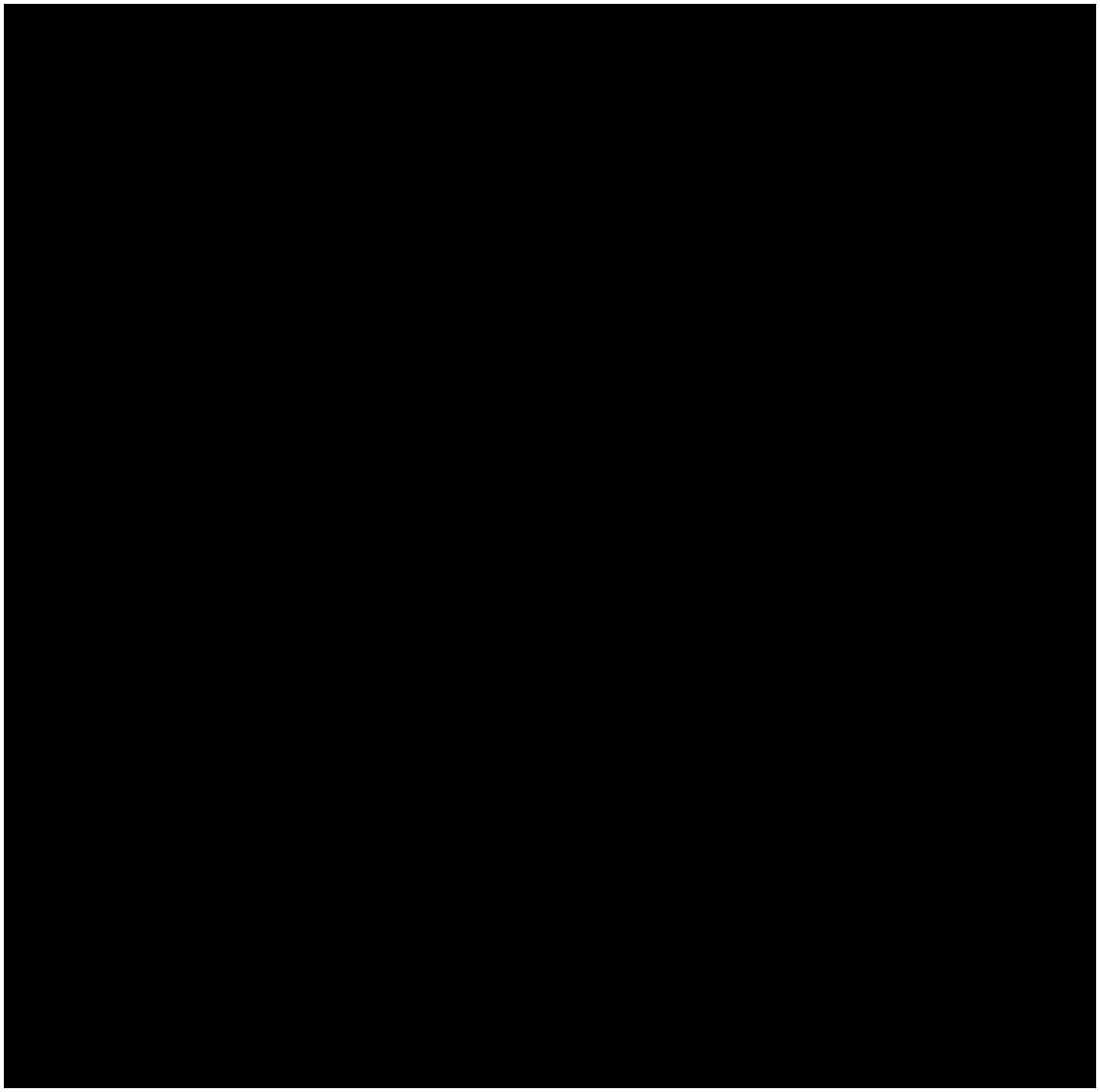
Figure 27: Selected OS curve fits

B.3.3.4. Progression-free survival

B.3.3.4.1. Nivolumab-relatlimab and nivolumab

Figure 28 presents the PFS KM data for all patients in RELATIVITY-047 and the corresponding underlying number at risk over time in the nivolumab-relatlimab and nivolumab arms of the trial. As shown by the Kaplan-Meier plot, PFS is similar across both treatment arms for an initial period of around 3 months. After this initial period, the PFS curves diverge, with the observed risk of progression lower in the nivolumab-relatlimab arm. This point at which PFS begins to diverge coincides with the first radiological assessment at 3 months, as outlined in the trial protocol. The KM curve begins to plateau for both treatment arms at around 40 months, aligning with long-term data published from other immunotherapies in melanoma (see Section B.3.3.2.1). The number of events and level of maturity of PFS are presented in Table 33.

Figure 28: RELATIVITY-047 progression-free survival, Kaplan–Meier curves



Key: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[51]

Table 33: Number of events and level of maturity of PFS in RELATIVITY-047

Endpoint	Outcome	Nivolumab-relatlimab (n = 355)	Nivolumab (n = 359)
PFS	Number of events	[redacted]	[redacted]
	Maturity (%)	[redacted]	[redacted]
Key: PFS, progression-free survival.			

B.3.3.4.1.1. Standard parametric models

Similar to the OS data (Section B.3.3.3), an unstratified analysis of the PFS KM data appears justified from Figure 28. This approach is also consistent with the use of time-varying HRs in the NMA (Section B.2.9). Cumulative hazard and Schoenfeld residuals plots for PFS, shown in Appendix O, are similarly indicative.

Following a similar analytical approach taken to the OS analysis in Section B.3.3.3, the range of 'standard' parametric survival models noted in NICE DSU TSD 14 (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma) were tested for PFS.[86] An overlay of the independent one-piece parametric models and observed KM data from RELATIVITY-047 and CheckMate-067 are shown in Figure 29 and Figure 30 for nivolumab and nivolumab-relatlimab, respectively. Appendix O provides further details of corresponding smoothed hazards and AIC and BIC statistics.

Based on an assessment of the single-fitted curves against the observed data from RELATIVTY-047, it is clear that the independent one-piece parametric survival curves are inappropriate for decision-making. In both treatment arms, generalised gamma and Gompertz models demonstrate a reasonable visual fit to the observed KM and smoothed hazards. However, it is evident that all standard parametric models struggle to capture the initial fall in survival at 3 months. This emphasises the importance of exploring more accurate methods of modelling progression-free survival across both treatment arms, which are discussed in subsequent sections.

Figure 29: PFS independent one-piece parametric survival curves for nivolumab

Figure 30: PFS independent one-piece parametric survival curves for nivolumab-relatlimab

B.3.3.4.1.2. Piecewise models

Alternative survival models were explored to improve the validity of PFS extrapolations for nivolumab-relatlimab and nivolumab. Consistent with guidance published in NICE DSU TSD 14 and 21, independent piecewise models were analysed.[86, 87] These provided a substantially better fit to the observed data as they reflect the trial-driven drop in PFS at 3 months (due to assessment of progression at this time) and are therefore preferable for the base-case analysis. An overlay of the independent piecewise models and observed KM data from RELATIVITY-047 and CheckMate-067 are shown in Figure 32 for nivolumab and Figure 34 for nivolumab-relatlimab. Corresponding smoothed hazards are shown in Figure 33 and Figure 35, respectively. The AIC and BIC statistics corresponding to the independent piecewise models fitted to RELATIVITY-047 are provided in Table 34.

Selection of the KM cut-off

Models fitted from baseline struggled to capture the initial 3 months of the KM curve for PFS, as the treatment arms sharply drop in line with each other before diverging (Figure 28). This is influenced by the trial protocol, as the first radiological assessment occurs 12 weeks after randomisation. Due to this, a pragmatic approach to model PFS is a piecewise model with a 3-month cut-point. This uses PFS KM data for the first 3 months, with standard parametric models fitted from 3 months onwards.

The use of a 3-month cut-point is justified by analysing the hazards, shown in Figure 31. The hazards reach an initial peak at 2.26 months for nivolumab and 2.27 months for nivolumab-relatlimab, respectively. Cumulative hazards also diverge from around 3 months (Appendix O). Thus, the use of a 3-month cut-point ensures models are fit after the point where the hazards have peaked and a difference between the two treatment arms is apparent, also whilst ensuring sufficient data are available to inform the extrapolation. This cut-point is further supported by a Chow structural change test. At 3 months, the Chow structural change test gives a p-value of < 0.0001 for nivolumab-relatlimab and $p = 0.0117$ for nivolumab, suggesting a change in the hazards at this point. Therefore, 3 months was selected as an appropriate cut-off, where 194 out of 359 patients were at risk in the nivolumab arm and 221 out of 335 patients were at risk in the nivolumab-relatlimab arm.

Figure 31: PFS hazards (nivolumab and nivolumab-relatlimab)

Figure 32: PFS piecewise parametric curve fits for nivolumab

Figure 33: PFS independent piecewise hazard plots for nivolumab (re-based to time zero)

Figure 34: PFS piecewise parametric curve fits for nivolumab-relatlimab

Figure 35: PFS independent piecewise hazard plots for nivolumab-relatlimab (re-based to time zero)

Table 34: Fit statistics of PFS independent two-piece survival extrapolation

Treatment	Nivolumab-relatlimab		Nivolumab	
Extrapolation	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Selection of the distribution for extrapolation beyond 3 months

Similarly to OS, for both treatment arms, the Gompertz model exhibits the best visual fit to the observed RELATIVITY-047 KM data and smoothed hazards, with all other models overestimating PFS towards the end of follow-up. The goodness of fit of the Gompertz is also similar to that of the other models, with a relative difference in AIC and BIC values of less than 1% compared with the best-fitting model.

In addition, as noted for OS, the Gompertz model is the only standard parametric model that provides a plateau in PFS for both treatments. As a plateau is observed in studies with long-term follow-up (Section B.3.3.2.1), the Gompertz is the only model to provide clinically plausible extrapolations, and which is able to model appropriately the underlying hazards.

Results of the adjusted ITC presented in Section B.2.9.2 demonstrate that the PFS for nivolumab-relatlimab (from RELATIVITY-047) is similar to that observed for nivolumab + ipilimumab (from CheckMate-067; statistically non-significant HR of [redacted], 95% CI [redacted] to [redacted]). This result is supported by the NMA (e.g. statistically non-significant HRs of [redacted] to [redacted] from Months [redacted] to [redacted]). Similarly, the adjusted ITC demonstrates comparability across the nivolumab arms of both trials (statistically non-significant HR of [redacted], 95% CI [redacted] to [redacted]). Therefore long-term data from CheckMate-067 was used to inform the plausibility of the long-term extrapolations from RELATIVITY-047. This comparison demonstrated that all of the standard parametric models underestimate long-term survival for both treatments when compared with long-term CheckMate-067 data, with the Gompertz displaying the closest alignment (the Gompertz-modelled decline in PFS hazard towards general population hazards demonstrated in Figure 35 mirrors the observed decrease in PFS hazard in Figure 21).

- CheckMate-067 demonstrates that for patients treated with nivolumab, the 7.5-year PFS rate is 27% (Figure 19).[35, 90] Most survival models explored predicted 7.5-year PFS rates ≥10% lower than this, with the highest survival rate being produced by the Gompertz model ([redacted]% and [redacted]% for the piecewise and standard versions, respectively); landmark PFS probabilities are detailed in Appendix O.
- Whilst the piecewise and standard (one-piece) Gompertz models both provide similar extrapolations, as noted previously the standard model provides poor within-sample fit, hence preference is given to the piecewise version.
- CheckMate-067 demonstrates that for patients treated with nivolumab + ipilimumab, the 7.5-year survival rate is 33% (Figure 19). Most survival models predicted 7.5-year PFS rates for patients treated with nivolumab-relatlimab ≥10% lower than this, with the highest survival rate being produced by the Gompertz model ([redacted]% and [redacted]% for the piecewise and standard versions, respectively).

To conclude, in both treatment arms, the 'plateauing effect' presented by the Gompertz model most closely captures the expected long-term progression-free survival of these patients and is most closely aligned with clinical expectation for patients receiving a PD-L1 treatment in this indication.[37] However, as shown below in Section B.3.3.4.4, PFS extrapolations for nivolumab-relatlimab generated by the Gompertz model do not align with the long-term outcomes for nivolumab + ipilimumab, as would be expected based on the above arguments. Instead, extrapolated PFS for nivolumab-relatlimab is at a much lower level than nivolumab + ipilimumab. This suggests that extrapolations for nivolumab-relatlimab are likely to underestimate the true long-term PFS of nivolumab-relatlimab, and hence also underestimate its true cost-effectiveness.

B.3.3.4.1.3. Spline models

Due to the poor fit of standard parametric models, spline-based models were also considered. Consistent with guidance published in NICE DSU TSD 14 and 21, independent spline models were fitted to RELATIVITY-047 data.[86, 87] Full details regarding the construction of spline models for PFS are provided in Appendix O. An overlay of the independent spline models and observed KM data from RELATIVITY-047 and CheckMate-067 are shown in Figure 36 for nivolumab and Figure 37 for nivolumab-relatlimab. Appendix O provides further details of corresponding smoothed hazards and AIC and BIC statistics.

In the nivolumab arm, all spline models demonstrate a good fit to the nivolumab KM and smoothed hazards, but do overestimate hazards initially. All spline models demonstrate very similar survival and hazards to each other over a 20-year period.

In the nivolumab-relatlimab arm, all spline models demonstrate a reasonable fit to the nivolumab-relatlimab KM and smoothed hazards. The 1-knot spline models present a marginally better fit to the smoothed hazards than the 2-knot models. As illustrated in the nivolumab arm, the spline models all demonstrate very similar survival and hazards over a 20-year period.

Spline models present an alternative to the piecewise Gompertz, with more conservative estimates (do not present the expected long-term plateau), but still demonstrate survival more in line with CheckMate-067 and clinical expectation than

the other piecewise models and standard parametric models. In account of this, a spline model for each treatment arm was explored in scenario analyses (Section B.3.10.2).

Priority was given to retaining the same model type (number of knots and scale) between the arms, following the advice given in the NICE DSU TSD 14.[86, 87] When determining the number of knots among equally well-fitting models, preference was given to lower numbers of knots to ensure that the long-term extrapolations are based on a reliable and sufficient number of events while avoiding over-fitting to the data. Thus, '1 knot – odds' was selected on both treatment arms in scenario analyses based on good visual fit to the PFS KM, smoothed hazards, statistical fit and long-term extrapolation on each arm.

Figure 36: PFS spline fits for nivolumab

Figure 37: PFS spline fits for nivolumab-relatlimab

B.3.3.4.2. Nivolumab + ipilimumab

In consistency with the approach taken in the analysis of OS, in the base case NMA fractional polynomials were used to model nivolumab + ipilimumab PFS.

The model selection process concluded that the best-fitting model was the second-order fractional polynomial (P_1=0, P_2=-1, scale and second shape) (Section B.2.9.1). Trial-specific KM curves overlaid with the modelled survival curves from the best-fitting distribution are available in Appendix O. It is evident that the nivolumab + ipilimumab fractional polynomial curve presents internal validity, providing a plausible fit to the observed PFS data in CheckMate-067. Cumulative survival over time was estimated by applying the nivolumab + ipilimumab HRs generated from the NMA to a reference modelled survival function using nivolumab as the reference treatment (piecewise Gompertz model, as detailed in Section B.3.3.4.1.2).

The nivolumab + ipilimumab curve produced captures the expected long-term PFS of these patients and aligns with clinical opinion on the expected plateau in PFS (Figure 38).[37]

B.3.3.4.3. Pembrolizumab

Consistent with the approach taken in the analysis of OS, in the base case pembrolizumab PFS was estimated by relative treatment effects from the NMA, with an assumption of equal clinical outcomes to nivolumab explored in a scenario analyses (Section B.3.10.2).

B.3.3.4.4. Summary of PFS base-case selections

The most appropriate and clinically plausible models for PFS are used in the base case, acknowledging that extrapolations for nivolumab-relatlimab are likely to underestimate true PFS. The models are summarised in Table 29 and illustrated in Figure 38.

- For nivolumab-relatlimab and nivolumab, the piecewise Gompertz model (KM + Gompertz [3 months]) was used. This provides a plausible fit to the observed data and, given the noted limitations, provides a clinically plausible long-term extrapolation
- For nivolumab + ipilimumab and pembrolizumab, PFS was estimated based on relative treatment effects estimated in the NMA, which are represented by time-varying HRs relative to nivolumab

For base case model selection, clinical plausibility was assessed via consistency with longer-term data from related sources (where appropriate) which was validated by UK clinical experts in an advisory board.[37] Alternative plausible assumptions were tested in scenario analyses (Section B.3.10.2). For all analyses, PFS is restricted to not exceed OS.

Figure 38: Selected PFS curve fits

B.3.3.5. Time to discontinuation

As described in Section B.3.2.3, all IO treatments are administered up to a treatment duration of 2 years. Therefore, TTD for the intervention and each of the comparators is capped at 2 years in the cost-effectiveness analysis base case. This stopping rule affects drug acquisition and administration costs as well as AE costs (Section B.3.5.1 and B.3.5.3). A limit to TTD being unable to exceed PFS was also included in the base case, so that no patients remain on 1L treatment post-progression, in line with UK clinical practice.[37]

B.3.3.5.1. Nivolumab-relatlimab and nivolumab

TTD is modelled based on RELATIVITY-047 to determine the cohort of patients remaining on treatment at each model cycle to accurately accrue treatment-related costs. Median TTD for nivolumab-relatlimab and nivolumab are presented in Table 35.

Table 35: RELATIVITY-047 median TTD

Treatment	Weeks	Months
Nivolumab-relatlimab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Key: TTD, time to discontinuation		

B.3.3.5.1.1. Standard parametric models

An overlay of the independent one-piece parametric models to observed KM data from RELATIVITY-047 are shown in Figure 39 for nivolumab and Figure 40 for nivolumab-relatlimab. AIC and BIC statistics corresponding to the parametric models fitted to RELATIVITY-047 are provided in Table 36.

Figure 39: TTD parametric curves for nivolumab

Figure 40: TTD parametric curves for nivolumab-relatlimab

Table 36: AIC and BIC statistics for survival model fits to RELATIVITY-047 TTD data

Treatment	Nivolumab-relatlimab		Nivolumab	
Extrapolation	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.				

The Weibull model provides a good visual fit to observed data from RELATIVITY-047 for both nivolumab and nivolumab-relatlimab treatment arms (Figure 39 and Figure 40), with plausible extrapolations. The Weibull model also has the best statistical fit of all models in both treatment arms (Table 36); hence, it is used to model TTD in the model. For nivolumab, the Weibull model aligns closely with the observed TTD KM from the nivolumab arm of CheckMate-067.

Similarly, the generalised gamma and gamma models also demonstrate good visual fits to the observed data and provide plausible long-term extrapolations in both treatment arms. Alternative models were explored in scenario analyses (Section B.3.10.2).

B.3.3.5.2. Nivolumab + ipilimumab

For nivolumab + ipilimumab, KM data are available for 5 years from CheckMate-067, which is almost fully mature ([redacted]% complete).[97] Thus, the KM was used directly to model TTD for the nivolumab component of this combination therapy (Figure 41).

Figure 41: TTD Kaplan–Meier curve for nivolumab + ipilimumab (CheckMate-067)

The duration of treatment with ipilimumab was modelled using the proportion of patients receiving each number of doses of ipilimumab. Proportions were obtained from the NICE Melanoma HEMR (originally derived from CheckMate-067) (Table 37).[77]

Table 37: Number of doses of ipilimumab received in combination with nivolumab

Total number of doses	Proportion of patients
One dose	5.1%
Two doses	10.0%
Three doses	15.4%
Four doses	69.5%

B.3.3.5.3. Pembrolizumab

KM data for TTD from KEYNOTE-006, the pivotal trial for pembrolizumab, were not readily available, and published articles of the trial were limited to reporting the median TTD only and did not disaggregate between line of therapy. In the absence of appropriate data from an RCT for pembrolizumab, pembrolizumab TTD was assumed equal to nivolumab in the base case (i.e. the nivolumab TTD reference

curve). This selection was supported by clinical expert opinion that the TTD for pembrolizumab and nivolumab is highly similar in clinical practice.[37]

In scenario analyses (Section B.3.10.2), a KM curve obtained from the NICE Melanoma HEMR, originally retrieved from PLD from the Systemic Anti-Cancer Therapy (SACT) database, was used to model pembrolizumab TTD.[77] Whilst there are limitations with comparing trial evidence on TTD to real-world evidence on TTD, including SACT data for just pembrolizumab (and using trial data for the remaining treatments) was considered an appropriate scenario given that a) the SACT database collects systemic anti-cancer therapy activity from all NHS England providers and b) the KM data were almost fully mature (98% complete). Further details of the SACT data for pembrolizumab are provided in Appendix O.

B.3.3.5.4. Summary of base-case selections for TTD

The most appropriate and clinically plausible models for TTD are used in the base-case analysis, as summarised in Table 30 and illustrated in Figure 42.

- For nivolumab-relatlimab and nivolumab, the Weibull model was used. This provides a plausible fit to the observed data, the best statistical fit, and a clinically plausible long-term extrapolation
- For nivolumab + ipilimumab, the nivolumab component was modelled using the near-complete TTD KM from CheckMate-067 and the ipilimumab component was modelled based on doses received in CheckMate-067
- For pembrolizumab, the nivolumab reference curve (Weibull model) was used and considered clinically plausible

Alternative models and extrapolation methods were tested in scenario analyses Section B.3.10.2.

The following scenarios were explored on each treatment arm simultaneously:

- TTD uncapped by PFS (i.e. TTD can exceed PFS)
- Treatment stopping rule at 5 years
- 10% of patients continue treatment beyond 2 years (based on UK clinical expert opinion regarding the continuation/re-initiation of IO treatment in a small proportion of patients)[37]

Figure 42: Selected TTD curve fits

Key: IO, immuno-oncology; PFS, progression-free survival; TTD, time to treatment discontinuation.
Note: These curves account for the 2-year IO stopping rule and limit of TTD to PFS.

B.3.3.6. Treatment-effect waning

Due to their mechanisms of action, the clinical effect of IO therapies extends beyond a patient completing their treatment, providing long-term survivorship in a subset of patients. The strong long-term evidence reflecting this is presented in Section B.3.3.2.1, which demonstrates heterogeneity in survival for melanoma patients with persistent treatment effects for multiple years after stopping treatment for a proportion of patients. In particular, long-term follow-up for CheckMate-067 demonstrates that there is a subset of long-term survivors for which the observed hazards for both PFS and OS eventually meets that of the general population.[85, 92-95] In particular, cure modelling indicated that for OS, the proportion of long-term survivors was 16-26% for ipilimumab (dependent on the parametric model used), 38–46% for nivolumab, and 49–54% for nivolumab + ipilimumab. Corresponding ranges for long-term PFS were 9-13% for ipilimumab, 29–33% for nivolumab and 38–40% for nivolumab + ipilimumab. This concept of long-term survivorship for IO melanoma treatments, along with the improvement in long-term survivorship with combination treatment, was supported by UK clinicians, who saw no reason why nivolumab-relatlimab would be any different.[37]

Whilst some trials allowed for treatment beyond 2 years, this is unlikely to affect long-term survivorship in clinical practice, as this has been observed both in trials with a 2-year stopping rule and also amongst patients who discontinued IO treatment early due to AEs.[89, 98] These findings are also supported by real-world evidence, which demonstrated durable response after discontinuation of anti-PD-1 monotherapy prior to 2 years,[99] as well UK clinician feedback on their experience with using IO treatments in melanoma.[37]

Within the economic model, the more effective combination immunotherapies (nivolumab-relatlimab and nivolumab + ipilimumab) lead to hazards reaching general population levels sooner than the monotherapies. For example, for OS, hazards intercept with general population hazards at 101, 109, 117, and 124 months for nivolumab-relatlimab, nivolumab + ipilimumab, nivolumab, and pembrolizumab, respectively. After this time-point, hazards increase due to population ageing. This leads to a natural waning of the relative treatment effect for two reasons.

First, there is a period during which the hazard for the more effective treatments increases, whilst the hazard is still decreasing for the less effective treatments (for example, there is a period of about 2 years during which the nivolumab-relatlimab hazard increases whilst the pembrolizumab hazard decreases).

Secondly, once all hazards have reached general population mortality, all subsequent treatments have the same hazard, and so there is no further relative treatment effect. Because this treatment waning occurs within the time-frame of observed long-term evidence, as demonstrated in Section B.3.3.2.1, there is no need to explore any further treatment waning scenarios as these would represent implausible situations. Graphs of the modelled hazards for OS and PFS capped by general population mortality are provided in Figure 43 and Figure 44, respectively (note that the y-axis of the latter is truncated to focus on the intersection of hazards with general population mortality).

Figure 43: Implemented overall survival hazards

Figure 44: Implemented progression-free survival hazards

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

As detailed in Section B.1.3.2, the physical symptoms of melanoma include pain, fatigue, weight loss, loss of appetite, nausea and shortness of breath. Alongside physical symptoms, melanoma impacts psychological functioning. Approximately one-third of patients with melanoma experience considerable levels of distress. As the disease progresses, patients begin to decline in almost all of the major functional

areas assessed by the HRQL scales, aligning with an increase in symptoms of their disease and the adverse effects of the therapies used to treat the illness.[31]

HRQL was evaluated in the RELATIVITY-047 trial using the EQ-5D-3L questionnaire. The NICE guidelines stipulate that the EQ-5D questionnaire is the preferred instrument for measuring changes in the HRQL alongside a clinical trial and that data collected directly from patients alongside a clinical study should be used to estimate the utility weights to populate the economic model.

B.3.4.2. Mapping

Utilities were evaluated using EQ-5D-3L questionnaire responses directly from patients from the RELATIVITY-047 trial, which is consistent with the NICE reference case. Therefore, no mapping was required.[83]

B.3.4.3. Health-related quality-of-life studies

An SLR was conducted to identify evidence for utility and HRQL in advanced, metastatic or unresectable melanoma. Searches were run in January 2022 and further updated in November 2022. Full details of the review are provided in Appendix H.

There were 18 studies identified that reported utility outcomes, of which 15 used a form of the EQ-5D questionnaire. Potentially useful studies for this analysis are those that report utility values, either by progression status or TTD. Therefore, we have focused on the four studies reporting this data; these are summarised in Table 38.

Table 38: Summary of identified studies reporting utility values, either by progression status or TTD

Author, year (NCT/trial acronym)	Title	Geographic scope	Intervention/ comparator	Type of data reported (HRQL/Utilities)
Franken, M, 2022[100]	Quality of life in advanced melanoma patients in the era of novel immune- and targeted therapies	The Netherlands	NR	HRQL and Utilities
Franken, M, 2022a[101]	Health state utilities of advanced melanoma patients treated in clinical practice in the era of novel immune- and targeted therapies	The Netherlands	Systemic treatment / NA	Utilities
Franken, M, 2022b[102]	Validity of the EQ-5D-3L and EQ-5D-5L in advanced melanoma	The Netherlands	Systemic treatment / NA	Utilities
Kandel, M, 2020[103]	Quality-of-life assessment in French patients with metastatic melanoma in real life	France	NR	HRQL and Utilities

Key: HRQL, health-related quality of life; TTD, time to treatment discontinuation.

In addition, six previous NICE appraisals for the treatment of advanced melanoma were hand-searched for HRQL data (Table 39), with results broadly demonstrating consistency with the analysis in this appraisal – suggesting these values are robust and valid for decision-making.

Table 39: HRQL data from previous NICE appraisals for the treatment of melanoma

NICE TA	Indication	Intervention	PFS utility	PD utility	Notes
TA319[78]	Previously untreated advanced (unresectable or metastatic) melanoma	Ipilimumab	Redacted	Redacted	Reported EQ-5D utilities in line with NICE reference case.
TA366[42]	Advanced melanoma not previously treated with ipilimumab	Pembrolizumab	0.82	0.71	Reported EQ-5D utilities in line with NICE reference case.
TA384[43]	Advanced (unresectable or metastatic) melanoma	Nivolumab	0.7892	0.7548	
TA396[79]	Unresectable or metastatic melanoma	Trametinib + dabrafenib	Trametinib + dabrafenib: 0.837 Vemurafenib: 0.746 Dabrafenib: 0.789	0.697	Used weighted averages of trametinib + dabrafenib in the data set. Calculated a difference in weighted average of pre-progression utilities between comparators and trametinib + dabrafenib.
TA400[41]	Advanced melanoma	Nivolumab + ipilimumab	0.7954	0.7625	Based on statistical models fitted using EQ-5D data collected in CheckMate-067 trial
TA410[80]	Unresectable or metastatic melanoma	Talimogene laherparepvec	Partial response: 0.77 Stable disease: 0.77	0.68	

Key: NICE, National Institute of Health and Care Excellence; PD, progressed disease; PFS, progression-free survival; TA, technology appraisal.

B.3.4.4. Adverse reactions

As noted in Section B.2.3.2, HRQL was evaluated prior to dosing in each 4-week treatment cycle. As such, it is likely that the within-trial EQ-5D data will not capture the impact of AEs. To capture this increased burden on patients, utility decrements for included AEs are applied. Hence, all Grade 3+ AEs by treatment with > 1% incidence across any arm have been included in the analysis, with the number and proportion of patients who experienced AEs shown in Table 40.

In the base case analysis, incidence and duration of AEs were derived from the pivotal trials or literature sources. Incidence of TRAEs was taken from RELATIVITY-047 for nivolumab-relatlimab and nivolumab, Larkin et al. (2019) (CheckMate-067)[98] or nivolumab + ipilimumab, and Robert et al. (2019) (KEYNOTE 006) for pembrolizumab.[89] This approach is consistent with assumptions made in the most recent NICE appraisals in previously untreated, metastatic melanoma.[41, 82]

It is evident that the incidence of Grade 3+ TRAEs is greater in patients receiving nivolumab + ipilimumab treatment, relative to any other treatment. In validation, clinical experts noted that AE incidence reported from KEYNOTE-006 (not presented [NP] and accounted for as 0%) lacked face validity.[37] Thus, incidence of Grade 3+ TRAEs included for pembrolizumab can be considered conservative.

Table 40: Incidence of treatment-related Grade 3–4 AEs for patients on each treatment arm

Adverse event	Nivolumab-relatlimab	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab
Fatigue	[redacted]	[redacted]	13	4
Skin reaction	[redacted]	[redacted]	22	1
Diarrhoea	[redacted]	[redacted]	30	10
Nausea	[redacted]	[redacted]	7	1
Vomiting	[redacted]	[redacted]	7	NP
Colitis	[redacted]	[redacted]	26	NP
Decreased appetite	[redacted]	[redacted]	4	NP
Adrenal insufficiency	[redacted]	[redacted]	NP	NP
Increased lipase	[redacted]	[redacted]	34	NP

Adverse event	Nivolumab-relatlimab	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab
Alanine transferase increased	[redacted]	[redacted]	19	NP
Aspartate transferase increased	[redacted]	[redacted]	27	NP
Source	RELATIVITY-047 (CA224-047)[51]	RELATIVITY-047 (CA224-047)[51]	CheckMate-067 (Larkin et al 2019)[98]	KEYNOTE-006 (Robert et al 2019)[89]
Key: AE, adverse event; NP; not published				

Utility decrements for each included AE were sourced from the literature and are presented in Table 41. Applying the utility decrements to the per-cycle probability of each AE (and its duration) produced the utility impact per cycle. AE cycle decrements for each treatment arm are presented in Table 42. It should be noted that the AE decrements across all treatment arms may be considered conservative given clinical expert opinion on the notable cumulative impact of Grade 1–2 AEs on patient quality of life.[37] This was considered particularly relevant for patients receiving nivolumab + ipilimumab treatment, as widely cited in the literature.[104]

Table 41: Event utility decrements of modelled drug-related AEs

Adverse event	Event utility decrement	Source
Fatigue	-0.110	Bregman et al. 2020[105]
Skin reaction	-0.030	Paly 2020[106]
Diarrhoea	-0.060	Bregman et al. 2020[105]
Nausea	-0.070	Bregman et al. 2020[105]
Vomiting	-0.070	Bregman et al. 2020[105]
Colitis	-0.130	Paly et al. 2020[106]
Decreased appetite	-0.070	Assumed equal to vomiting
Adrenal insufficiency	-0.050	Assumed equal to elevated liver enzymes
Increased lipase	-0.050	Assumed equal to elevated liver enzymes
Alanine transferase increased	-0.050	Barbier et al. 2022 [107]
Aspartate transferase increased	-0.050	Barbier et al. 2022 [107]

Table 42: Per-cycle utility impact of modelled AEs

Regimen	Utility impact per model cycle (month)
Nivolumab-relatlimab	-0.00011855
Nivolumab	-0.00006234
Nivolumab + ipilimumab	-0.00134380
Pembrolizumab	-0.00005452

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

In line with the NICE reference case[83], the utility values underpinning the cost-effectiveness analysis are based on HRQL measured directly by patients using the EQ-5D-3L questionnaire (collected within RELATIVITY-047), and valued using public preferences as per the UK time trade-off (TTO) valuation set used in many previous appraisals. Utilities used in the cost-effectiveness analysis are also age-adjusted using the Hernández-Alava algorithm.[108] A scenario tests the impact of not using age-adjustment (Section B.3.10.2).

Table 43 summarises the utility values used in the cost-effectiveness analysis.

Table 43: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case				
PF	[redacted]	[redacted]	Section B.3.4.5.1	Estimated directly from RELATIVITY-047 EQ-5D data[51], in line with the NICE reference case.[83] Progression-based approach utilises progression status typically assessed in clinical practice
PD	[redacted]	[redacted]		
AE decrements				
Fatigue	-0.110	NA		Section B.3.4.4

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Skin reaction	-0.030	NA	Section B.3.4.4	
Diarrhoea	-0.060	NA		
Nausea	-0.070	NA		
Vomiting	-0.070	NA		
Colitis	-0.130	NA		
Decreased appetite	-0.070	NA		
Adrenal insufficiency	-0.050	NA		
Increased lipase	-0.050	NA		
Alanine transferase increased	-0.050	NA		
Aspartate transferase increased	-0.050	NA		
Key: AE, adverse event; NA, not applicable; PD, progressed disease; PF, progression-free				

B.3.4.5.1. Base case analysis: utilities by health state

The utility values in the economic model are driven by progression status and are applied to all treatment arms, independent of treatment choice.

The effect of disease progression and treatment status on HRQL was formally assessed using linear mixed-effects models fitted to the ITT population. A subject ID random effect was included to reflect the fact that each patient provides multiple values. The least-squared mean estimates of the mixed-effects model including only a fixed effect for progression status alongside the random effect for subject ID are shown in Table 44. The progressed disease state had a statistically significant lower utility ($p < 0.0001$), with an estimated mean utility of 0.74 compared to 0.77 for the progression-free state.

Table 44: Economic model health state values – base case (RELATIVITY-047)

Health state	Estimate
Progression-free	[redacted]
Progressed	[redacted]
Death	0.000
Source: RELATIVTY-047[51]	

Clinical experts consulted at an advisory board held the view that there would be a greater difference in utility estimates between the PF and PD health states, which may not have been captured by mean utility estimates calculated from RELATIVTY-047 (difference of 0.030 between PF and PD states).

Potential reasons provided for the lower-than-expected decrement upon progression included: EQ-5D may not be sensitive enough to capture differences within melanoma; the impact of a progression event may be limited due to it being based on radiological progression in RELATIVITY-047 and the limited follow-up of patients post-progression (and potentially those who are unwell not completing questionnaires).

Accounting for clinician comments, a scenario using the health state utilities that were used in the NICE Melanoma HEMR model was explored (Table 45).[77] Utility values were calculated by taking an unweighted average of values used in each health state from a basket of immunotherapy TAs in advanced melanoma. An unweighted average was considered appropriate as all values in the TAs were derived from the relevant trials, with none of them considered to be better or worse estimates. These utilities exhibited a difference of 0.065 between PF and PD states. To note, this scenario had minimal impact on the incremental cost-effectiveness ratio (ICER), presented in Section B.3.10.2.

Table 45: Economic model health state values – scenario analysis (NICE Melanoma HEMR)

Health state	All-risk cohort
Progression-free	0.779
Progressed	0.714
Death	0.000
Source: NICE Melanoma HEMR.[77]	

B.3.5. Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in January 2022 and further updated in November 2022 to identify healthcare costs and healthcare resource use (HCRU) associated with the treatment of unresectable, advanced melanoma. Full details of the SLR are presented in Appendix I.

The SLR identified 49 reports on healthcare cost and resource utilisation. None of the identified reports focussed solely on the UK. Six identified studies reported on the UK as part of multi-country research. These studies are summarised in Table 46. Two of the identified studies reported costs of with TRAEs associated with melanoma treatment, and are used in the economic model (see Section B.3.5.3).[109, 110] One study sought to identify treatment-specific costs, but this study did not include nivolumab-relatlimab. One reported costs associated with melanoma treatment prior to the availability of ipilimumab and vemurafenib.

In addition to studies identified by the SLR, the de novo analysis also draws on the approach used in TA400, which draws from data collected in the MELODY study.[41, 77]

Table 46: Summary of identified cost and resource use studies with UK data

	Country	Objective	Type of data
Grange, 2017[111]	France, Germany, UK	To estimate the cost-of-illness associated with completely resected stage IIIB/IIIC melanoma with macroscopic lymph node involvement, overall and by disease phase, in France, Germany and the UK.	Direct/Indirect costs & Resource use
Johnston, 2012[112]	France, Italy, UK	To characterise the country specific health care costs incurred by individuals with advanced melanoma prior to the availability of newly introduced treatments such as ipilimumab and vemurafenib throughout the course of disease following initial treatment with systemic therapy. To stratify costs incurred while receiving systemic therapy versus those incurred while receiving best supportive care only, and to compare overall and monthly costs between short-term and long-term survivors to assess the potential economic impact of extending survival.	Direct costs & Resource use
Potluri, 2019[113]	UK, Germany	To compare melanoma-specific costs following treatment with nivolumab + ipilimumab, nivolumab monotherapy, or ipilimumab monotherapy from the UK and German perspectives to ascertain whether these clinical benefits resulted in a cost advantage.	Direct costs
Vouk, 2016[109]	UK, Germany, France, Italy and Australia	To estimate per-event cost and economic burden associated with managing the most common and/or severe metastatic melanoma (MM) treatment-related adverse events (AEs) in Australia, France, Germany, Italy, and the UK.	Direct costs & Resource use
McKendrick, 2016[75]	Australia, Canada, France, Germany, Italy, the Netherlands, Spain, UK	To estimate healthcare resource use (HRU) associated with the treatment of metastatic melanoma, from treatment initiation to death, based on country-specific guidelines in Australia, Canada, and six European countries (France, Germany, Italy, the Netherlands, Spain, and the UK).	Resource use
Wehler, E., 2017[110]	Australia, Canada, France, Germany, Italy, the Netherlands, Spain, UK	To explore the costs in Italy, Spain, Germany, France, the Netherlands, the UK, Canada, and Australia related to managing the more frequent therapy-related toxicities to better understand the burden of AE-related economic impact.	Direct costs

Healthcare resource utilisation estimates used in the de novo analysis were validated by UK clinicians with experience of treating advanced, metastatic melanoma.[37]

B.3.5.1. Intervention and comparators' costs and resource use

Treatment costs are calculated based on the recommended dosing regimen for each treatment for the modelled treatment duration (Section B.3.3). Unit costs were obtained from the drugs and pharmaceutical electronic market information tool (eMIT) where possible. Where unit costs were not available from eMIT, the British National Formulary (BNF) and the Monthly Index of Medical Specialities (MIMS) were used.

Pembrolizumab and nivolumab have two options for dosing regimens. In the maintenance phase, nivolumab may be administered as 240 mg every 2 weeks, or 480 mg every 4 weeks. Pembrolizumab may be administered as 200 mg every 3 weeks or 400 mg every 6 weeks. UK clinicians stated that more frequent dosing would be avoided due to the greater burden on clinics and patients of additional administrations.[37] Therefore, the 4-weekly and 6-weekly schedules were used in the model.

The recommended dose per administration, administration schedule and list prices for each treatment are presented in Table 47 and Table 48. The regimen for nivolumab + ipilimumab differs between 'induction' and 'maintenance' periods; thus, per-cycle drug acquisition costs were modelled separately for the induction and maintenance periods.

Table 47: Dosing information

Regimen	Treatment	Dose (prescribed)	Dose in mg	Frequency description	Admin method	Dosing source
Nivolumab-relatlimab	Nivolumab-relatlimab	640 mg	640	Q4W	IV	RELATIVITY-047
Nivolumab	Nivolumab	480 mg	480	Q4W	IV	Nivolumab SmPC[44]
Pembrolizumab	Pembrolizumab	400 mg	400	Q6W	IV	Pembrolizumab SmPC[45]
Nivolumab + ipilimumab (induction)	Nivolumab	1 mg/kg	72.5	Q3W	IV	Nivolumab SmPC

Regimen	Treatment	Dose (prescribed)	Dose in mg	Frequency description	Admin method	Dosing source
Nivolumab + ipilimumab (induction)	Ipilimumab	3 mg/kg	217.5	Q3W	IV	Ipilimumab SmPC[46]
Nivolumab + ipilimumab (maintenance)	Nivolumab	480 mg	480	Q4W	IV	Nivolumab SmPC
Nivolumab + ipilimumab (maintenance)	Ipilimumab	N/A	N/A	N/A	N/A	Ipilimumab SmPC[46]
Key: IV, intravenous; Q3W, every three weeks; Q4W, every four weeks; Q6W, every 6 weeks; SmPC, summary of product characteristics.						

Table 48: Drug pack costs

Treatment	Pack size	Form	Quantity per unit	Cost per pack	Source (pack cost)
Nivolumab-relatlimab	1	16 mg/ml (vial)	20 ml	[redacted]	BMS confidential information
Nivolumab	1	10 mg/ml (vial)	4 ml	£439	MIMS[114] [Accessed 05/04/2023]
	1	10 mg/ml (vial)	10 ml	£1,097	MIMS[114] [Accessed 05/04/2023]
	1	10 mg/ml (vial)	24 ml	£2,633	MIMS[114] [Accessed 05/04/2023]
Ipilimumab	1	5 mg/ml (vial)	10 ml	£3,750	MIMS[114] [Accessed 05/04/2023]
Ipilimumab	1	5 mg/ml (vial)	40 ml	£15,000	MIMS[114] [Accessed 05/04/2023]
Pembrolizumab	1	25 mg/ml (vial)	4 ml	£2,630	MIMS[114] [Accessed 05/04/2023]
Key: mg, milligram; ml, millilitre; MIMS, Monthly Index of Medical Specialities					

Drug administration costs are accrued for the duration of treatment in each treatment arm (Section B.3.3.5). The unit costs of treatment administration are sourced from NHS reference costs 2020–21 (Table 49). Ipilimumab is assumed to incur no

administration cost in addition to the cost of administering nivolumab in alignment with TA400.[41]

Table 49: Drug administration unit costs

Administration type	Cost per administration (£)	Source
Oral*	0	Assumption
Intravenous	470.62	NHS Reference Costs 2020/21 - Deliver subsequent elements of a Chemotherapy Cycle [SB15Z]
Intravenous (induction)	526.52	NHS Reference Costs 2020/21 - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance [SB14Z]
Note: *Oral therapies are included in subsequent treatment (Section B.3.5.4.1)		

B.3.5.2. Health-state unit costs and resource use

In the base-case analysis, HCRU costs are based on the approach used in NICE TA400.[41] This approach was supported by comments from UK clinicians that strongly indicated that resource use is considered time-dependent and that monitoring of patients is de-escalated over time, rather than solely based on progression status. Progression status does still influence costs due to incurring subsequent treatment costs (Section B.3.5.4.1).

TA400 used data collected in the MELODY trial, with HCRU associated with the number of years a patient has been in the model and includes a one-off cost upon treatment initiation.[41] Per-cycle resource use estimates used in TA400 are presented in Table 50, and resource use associated with treatment initiation and palliative care is presented in Table 51 and Table 52. Table 53 and Table 54 summarise HCRU costs applied in this approach.

Table 50: TA400 per-cycle resource use

Resource use item	Year 1		Year 2		Year 3 and beyond	
	% Patients	Per cycle resource use	% Patients	Per cycle resource use	% Patients	Per cycle resource use
Medical oncologist consultation	79.3%	5.7	39.6%	5.7	23.8%	5.7
Radiation oncologist consultation	6.0%	3.0	3.0%	3.0	1.8%	3.0
GP consultation	4.0%	6.0	2.0%	6.0	1.2%	6.0
Brain MRI	18.0%	0.9	9.0%	0.9	5.4%	0.9
PET-CT scan	0.0%	1.2	0.0%	1.2	0.0%	1.2
Nurse visit	12.5%	3.0	6.3%	3.0	3.8%	3.0
Oncology general ward - inpatient	5.0%	3.9	2.5%	3.9	1.5%	3.9
Complete blood count	100.0%	3.9	50.0%	3.9	30.0%	3.9
Complete metabolic panel	95.0%	3.9	47.5%	3.9	28.5%	3.9
Lactate dehydrogenase	95.0%	3.9	47.5%	3.9	28.5%	3.9
CT scan (any)	100.0%	3.0	50.0%	3.0	30.0%	3.0
Bone scintigraphy	1.0%	0.9	0.5%	0.9	0.3%	0.9
Echography	9.0%	0.9	4.5%	0.3	2.7%	0.3
Chest x-ray	27.5%	3.3	13.8%	3.3	8.3%	3.3
Plastic surgeon consultation	2.0%	4.5	1.0%	4.5	0.6%	4.5

Key: CT, computerised tomography; GP, general practitioner; MRI, magnetic resonance imaging; PET, positron emission tomography.

In addition to per-cycle costs, the model applies a one-off cost on treatment initiation, and a cost of palliative care that is applied in the three cycles before death (see Table 54).

Table 51: TA400 one-off resource use on treatment initiation

Resource use item	Treatment initiation	
	% Patients	Resource use
Medical oncologist consultation	81.0%	3.6
Radiation oncologist consultation	6.0%	2.3
GP consultation	4.0%	2.0
Palliative care physician (consultation)	1.3%	1.0
Psychology specialist consultation	0.5%	1.0
Plastic surgeon consultation	2.0%	1.5
Inpatient stay (oncology/general ward)	6.0%	2.8
Complete blood count	100.0%	1.2
Complete metabolic panel	100.0%	1.2
Lactate dehydrogenase	100.0%	1.2
CT scan (any)	100.0%	1.0
Brain MRI	14.5%	1.0
PET-CT scan	5.0%	1.0
Bone scintigraphy	16.8%	1.0
Echography	4.5%	1.0
Chest x-ray	17.5%	1.0

Key: CT, computerised tomography; GP, general practitioner; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 52: TA400 palliative care resource use

Resource use item	Palliative care period (12 weeks before death)	
	% Patients	Per cycle resource use
Medical oncologist consultation	62.3%	2.7
Radiation oncologist consultation	7.0%	4.5
GP consultation	78.5%	5.7
Psychology specialist consultation	3.5%	9.0
Brain MRI	1.3%	3.0
Palliative care physician (consultation)	23.0%	4.2
Home aide (non-medical specialist) visit	25.5%	21.9
Oncology general ward - inpatient	13.0%	10.8
Palliative care unit - inpatient	24.5%	12.0
CT scan (any)	3.8%	3.0
Chest x-ray	1.3%	3.0
Morphine - Oral	51.0%	3.0
Morphine - IV	22.0%	3.0
Morphine - Transdermal patch	15.0%	3.0
NSAIDs (Ibuprofen)	47.5%	3.0
Other - Paracetamol	36.0%	3.0
Palliative care physician - home care	21.8%	3.0
Palliative care nurse - home visit	61.0%	4.2

Key: CT, computerised tomography; GP, general practitioner; IV, intravenous; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug.

Table 53: HCRU costs associated with model health states

Health state	Per cycle cost
Year 1	£1,976.40
Year 2	£985.80
Year 3+	£592.20
Terminal care (applied at death)	£7,679.48

Table 54: One-off HCRU costs

One-off HCRU	Per-cycle cost
Treatment initiation (applied in the first cycle)	£1,117.21
Palliative care (applied in the three cycles before death)	£3,496.40

Unit costs used to calculate HCRU costs implemented in the model were obtained from standard NHS reference costs[115] and the PSSRU 2021[116] and are detailed in Appendix O. Where unit costs were not available for the current cost year, they were inflated using the PSSRU NHSCII pay and prices inflation index, and the HCHS pay and prices index before 2014/15. These unit costs are multiplied by resource use estimates sourced from NICE TA400 to derive per-cycle costs and one-off costs upon treatment initiation, progression and death.

B.3.5.3. Adverse reaction unit costs and resource use

Modelled AE management costs are calculated based on the incidence and duration of Grade 3+ AEs observed in more than 1% of patients in any treatment arm. The included AEs and their incidence in each arm are presented in Section B.3.4.4.

AE unit costs were taken from NHS References Costs and PSSRU costs where possible; if unavailable, relevant literature sources were used. The costs applied for AEs are included in Table 55.

Per-cycle AE costs (Table 56) are applied for the duration of treatment in each arm. Given the relative difference in incidence of Grade 3+ TRAEs, the per-cycle AE cost incurred by patients receiving nivolumab + ipilimumab treatment is considerably greater than that incurred by patients in any other treatment arm.

Table 55: Adverse event costs

Adverse event	Cost per event	Source
Fatigue	£41.29	GP visit, per patient contact lasting 9.22minutes. PSSRU 2020/2021
Skin reaction	£647.53	NHS Reference Costs 2020/21 - Non-elective short stay, weighted average of [JD07A-K], Skin Disorders with and without Interventions, with CC Score 0-12+
Diarrhoea	£656.64	NHS Reference Costs 2020/21- Non-elective short stay, weighted average [FD10A-M], Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with Single Intervention and without Intervention with CC Score 0-8+
Nausea	£216.25	Average cost of total attendances, Outpatient, General Medicine
Vomiting	£210.52	Average cost of total attendances, Outpatient, General Medicine
Colitis	£3,335.35	Vouk et al. 2016[109]
Decreased appetite	£210.52	Average cost of total attendances, Outpatient, General Medicine
Adrenal insufficiency	£655.63	NHS Reference Costs 2020/21 - Non-elective short-stay, weighted average of [KA08A-C], Other Endocrine Disorders, with CC Score 0-4+
Increased lipase	£655.63	NHS Reference Costs 2020/21 - Non-elective short-stay, weighted average of [KA08A-C], Other Endocrine Disorders, with CC Score 0-4+
Alanine transferase increased	£667.35	NHS Reference Costs 2020/21 - Non-elective short-stay, weighted average of [SA08H-J], Other Haematological or Splenic Disorders, with CC Score 0-6+
Aspartate transferase increased	£667.35	NHS Reference Costs 2020/21 - Non-elective short-stay, weighted average of [SA08H-J], Other Haematological or Splenic Disorders, with CC Score 0-6+

Table 56: Per-cycle AE costs

Regimen	Cost per cycle
Nivolumab-relatlimab	£7.67
Nivolumab	£5.17
Nivolumab + ipilimumab	£126.24
Pembrolizumab	£2.28

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Subsequent therapy costs

Following progression on any of the modelled treatments, patients may receive further rounds of therapy. The cost of these subsequent therapies is applied as a one-off cost upon treatment discontinuation (Table 65), and was derived using the same approach as that applied in the recent NICE Melanoma HEMR.[77] The total cost is based on the proportion of patients receiving subsequent therapies, the distribution of each subsequent therapy, the duration of subsequent treatment and the acquisition and administration costs associated with each treatment. These are discussed in turn.

Proportion of patients receiving subsequent therapies

Evidence for the proportion of patients assumed to receive further rounds of therapy was available from RELATIVITY-047 (for nivolumab-relatlimab and nivolumab) and CheckMate-067 (nivolumab + ipilimumab and nivolumab) (Table 57). Subsequent therapy data from KEYNOTE-006 (pembrolizumab) was not reported in mature data cuts (i.e. past 2 years) and was thus deemed inappropriate to consider here, which is aligned with the approach in the NICE Melanoma HEMR.[77]

Table 57: Proportion of patients receiving subsequent therapy (RELATIVITY-047 and CheckMate-067)

First-line regimen	Patients receiving subsequent therapy (%)	Source
Nivolumab-relatlimab	[redacted]	RELATIVITY-047[51]
Nivolumab	[redacted]	RELATIVITY-047[51]
	59%	CheckMate-067; NICE Melanoma HEMR[77]
Nivolumab + ipilimumab	46%	CheckMate-067; NICE Melanoma HEMR[77]

In the base case, the proportions of patients receiving subsequent therapy are taken from the NICE Melanoma HEMR committee preferred approach, which is based on data from CheckMate-067 for nivolumab, nivolumab + ipilimumab, and pembrolizumab (assumed equal to nivolumab) (Table 58). In the absence of long-term data from RELATIVITY-047 (which is required to reliably estimate rates of

subsequent treatment), the proportion of patients for the nivolumab-relatlimab arm was assumed to fall between that cited in the HEMR report for nivolumab + ipilimumab (46%) and nivolumab (59%) when accounting for a higher proportion of patients discontinuing therapy due to a TRAE (Grade 3+) in the nivolumab-relatlimab arm versus the nivolumab arm of RELATIVITY-047 ([redacted]% versus [redacted]%, a difference of [redacted]%; Table 19). Therefore, the base case assumes [redacted]% of patients in the nivolumab-relatlimab arm will receive subsequent therapy (Table 58). A scenario is also provided assuming equal subsequent therapy for the nivolumab-relatlimab arms as with nivolumab (59%) (Section B.3.10.2); however, due to a lower rate of TRAEs and improved PFS versus nivolumab, future data cuts from RELATIVITY-047 are expected to show a lower proportion of patients receiving subsequent therapy with nivolumab-relatlimab.

During validation, UK clinicians indicated that the proportion of patients proceeding to a second line of treatment may be higher than what would likely be seen in UK clinical practice (due to trial inclusion criteria).[37] However, at present no UK real-world data with sufficient follow-up are currently available to model the proportion of patients who receive subsequent therapy in UK clinical practice. As noted in the NICE Melanoma HEMR (Section HE1.4.4.1), the real-world cohort by Sacco et al (2018) has very limited follow-up and the committee had concerns over the validity of the data that could not be resolved.[77,117] Therefore, a scenario has been provided where all treatment arms are assumed to have 20% lower subsequent treatment than the proportions used in the NICE Melanoma HEMR (Section B.3.10.2). This scenario remains consistent with the notion that dual IO therapies will have a lower proportion of patients receiving subsequent therapy. This can be attributed to improved PFS and lower rates of TRAE on dual IO therapy relative to IO monotherapy (as supported by both RELATIVITY-047 and CheckMate-067 [Section B.3.3.4]).

Table 58: Proportion of patients receiving subsequent therapy (base case)

First-line regimen	Patients receiving subsequent therapy (%)	Source

Nivolumab-relatlimab	[redacted]%	CheckMate-067; NICE Melanoma HEMR[77] and [redacted]% reduction based on Grade 3-4 TRAEs leading to discontinuation in RELATIVTY-047[51]
Nivolumab	59%	CheckMate-067; NICE Melanoma HEMR[77]
Nivolumab + ipilimumab	46%	CheckMate-067; NICE Melanoma HEMR[77]
Pembrolizumab	59%	CheckMate-067; NICE Melanoma HEMR[77]

Distribution of each subsequent therapy

The pivotal trials for the treatments included in the economic evaluation are all international and the observed distributions of subsequent therapy may not be reflective of UK clinical practice. This was highlighted as a particular issue in the NICE Melanoma HEMR, which used clinical input to derive a distribution of subsequent therapies that reflected UK clinical practice. It was considered that patients receiving nivolumab + ipilimumab first-line who are sufficiently fit to receive further systemic therapy would receive either chemotherapy if they tested as *BRAF*-wild type, or a targeted treatment if they tested as *BRAF*-mutant.[45, 77] For this appraisal, clinician feedback indicated that if a patient was fit to receive ipilimumab, they would be prescribed nivolumab + ipilimumab first-line. Given nivolumab-relatlimab represents another dual IO therapy, it was assumed that subsequent treatment options would be guided similarly to patients receiving nivolumab + ipilimumab in first-line. Patients receiving IO monotherapy would receive either ipilimumab if they tested *BRAF*-wild type, or a targeted treatment if they tested *BRAF*-mutant. This NICE Melanoma HEMR clinical algorithm was combined with the *BRAF* proportions in RELATIVITY-047 to derive the distribution of subsequent treatments by treatment arm (Table 59 and Table 60). The resulting estimates are provided in Table 61.

This approach was broadly agreed with by UK clinicians consulted at an advisory board.[37] It was noted by clinicians that chemotherapy would not often be used as a subsequent treatment and that such patients (originally receiving dual immunotherapy and *BRAF* wild-type [Table 59]) would be recruited for clinical trials. Given the costs of interventional treatments received in clinical trials are not typically incurred by the NHS, chemotherapy was maintained as a subsequent treatment option; this was considered a conservative estimate.

Table 59: Subsequent treatment clinical decision rules (adapted from the NICE Melanoma HEMR)

Subsequent treatment	**1L treatment**	
***BRAF* status**	**Nivolumab-relatlimab / nivolumab + ipilimumab**	**Nivolumab OR pembrolizumab**
Wild-type	Clinical trials (cost incurred by the NHS and PSS assumed to be represented by chemotherapy)	Ipilimumab
Mutant	BRAF+MEK inhibitor	BRAF+MEK inhibitor

Table 60: *BRAF* status of patients in RELATIVITY-047

Biomarker	**N**	**Proportion**
Overall	714	N/A
BRAF mutant	[redacted]	[redacted]%
BRAF wild-type	[redacted]	[redacted]%
Source: RELATIVITY-047[51]		

Table 61: Subsequent therapy distributions by treatment arm

Subsequent treatment	**Nivolumab-relatlimab**	**Nivolumab**	**Nivolumab + ipilimumab**	**Pembrolizumab**
Dabrafenib + trametinib	19.26%	19.26%	19.26%	19.26%
Encorafenib + binimetinib	19.26%	19.26%	19.26%	19.26%
Clinical trials (chemo-therapy [dacarbazine] assumed to represent cost)	61.48%	N/A	61.48%	N/A
Ipilimumab	N/A	61.48%	N/A	61.48%
Source: NICE Melanoma HEMR.[77]				

Duration of subsequent treatment

The duration of subsequent therapy was derived from the NICE Melanoma HEMR, with time on subsequent treatment after nivolumab-relatlimab assumed equal to that in the nivolumab + ipilimumab arm (Table 62).[45, 77] These values were validated by UK clinicians, who suggested that the available mean durations may be slightly higher than would be seen in clinical practice – an outcome that may be driven by use of targeted BRAF therapies.[37] The one exception to Table 62 is ipilimumab

monotherapy, for which a subsequent treatment duration of 3 months was used in line with the SmPC.[46]

Table 62: Subsequent therapy durations

Treatment	Mean time on subsequent treatment (months)	Source
Nivolumab-relatlimab	8.81	NICE Melanoma HEMR[77]
Nivolumab + ipilimumab	8.81	
Nivolumab	7.77	
Pembrolizumab	7.77	

Subsequent treatment costs and dosing

Each subsequent treatment regimen is associated with the same dosing, drug acquisition and administration cost as dosing in the initial line of therapy as described in Section B.3.5.1, where possible. Acquisition costs for each subsequent therapy are presented in Table 63 and dosing information is presented in Table 64. Administration costs are calculated in line with Section B.3.5.1.

Table 63: Subsequent therapy acquisition costs

Treatment	Pack size	Form	Strength per unit	Cost per pack	Source (pack cost)
Dabrafenib	28	Capsule	50 mg	£933.33	BNF[118] [accessed 12/04/23]
Trametinib	30	Tablet	2 mg	£4,800.00	BNF[118] [accessed 12/04/23]
Dacarbazine	10	Vials	100 mg	£58.86	eMIT[119] [accessed 05/04/23]
Encorafenib	28	Capsule	50 mg	£622.22	BNF[118] [accessed 12/04/23]
Binimetinib	84	Tablet	15 mg	£2,240.00	BNF[118] [accessed 12/04/23]

Table 64: Subsequent therapy dosing

Regimen	Treatment	Dose	Frequency (description)	Admin method	Source (dosing)
Dabrafenib-trametinib	Dabrafenib	150 mg	Twice daily	Oral	Dabrafenib SmPC[120]
	Trametinib	2 mg	Daily	Oral	Trametinib SmPC[121]
Dacarbazine	Dacarbazine	1,547 mg	850 mg/m2 body surface area on day 1 and then once every 3 weeks as intravenous infusion	IV	Dacarbazine SmPC[122]
Encorafenib-binimetinib	Encorafenib	450 mg	Daily	Oral	Encorafenib SmPC[123]
	Binimetinib	45 mg	Twice daily	Oral	Binimetinib SmPC[124]
Ipilimumab	Ipilimumab	239 mg	3 mg/kg Q3W	IV	Ipilimumab SmPC[46]
Key: IV, intravenous; Q3W, every three weeks; SmPC, Summary of Product Characteristics					

Table 65: Total subsequent treatment costs

Regimen	Subsequent treatment acquisition costs	Subsequent treatment administration costs
Nivolumab-relatlimab	£37,895.89	£3,798.46
Nivolumab	£62,122.91	£1,293.46
Nivolumab + ipilimumab	£37,895.89	£3,798.46
Pembrolizumab	£62,122.91	£1,293.46

B.3.6. Severity

Patients with untreated unresectable or metastatic melanoma experience worsening of both their expected length of life and quality of life. The expected general population QALYs for the modelled population were calculated in the model using ONS Life Tables and Hernández-Alava general population utilities.[96, 108] The QALY shortfall calculator developed by Schneider et al. 2022 was used to validate absolute and proportional QALY shortfall estimates using HRQL norms from the NICE reference case.[83] Patient characteristics used in the analysis were consistent with those informing the base-case economic analysis.

A summary of the QALY shortfall analysis is presented in Table 66. The expected discounted QALYs for people living with untreated unresectable or metastatic melanoma on current treatment are also detailed in Table 66, based on the model results described in Section B.3.9 below. This resulted in an absolute QALY shortfall of 6.53-7.75 and a proportional shortfall of 54.90-65.14%, depending on the treatment. As the absolute QALY shortfalls are all below 12 and the proportional QALY shortfalls are all less than 85%, no multiplier for disease severity is considered appropriate for any of the comparisons.

Table 66: Summary of QALY shortfall analysis

TA	Treatment	Starting age	Proportion male (%)	Expected total QALYs for the general population	Expected total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall (absolute/proportional)
ID1688	Nivolumab-relatlimab	61.2	58.3	11.891	N/A	N/A
	Nivolumab				4.774	7.12 / 59.85%
	Nivolumab + ipilimumab				5.363	6.53 / 54.90%
	Pembrolizumab				4.145	7.75 / 65.14%
Key: QALY, quality-adjusted life year.						

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B.3.7. Uncertainty

Uncertainty in the available evidence base has been thoroughly explored where possible through evaluation of the associated parameter uncertainty and testing of the various structural assumptions made within the economic model. The key areas of uncertainty in the economic analysis are considered to be the following:

- Whilst there are mature survival data for nivolumab, nivolumab + ipilimumab and pembrolizumab from the CheckMate-067 and KEYNOTE-006 trials, there is less evidence for the long-term outcomes of patients treated with nivolumab-relatlimab. However, nivolumab-relatlimab includes nivolumab (for which long-term evidence is available from CheckMate-067), and clinicians believed nivolumab-relatlimab to provide long-term survivorship (as seen with nivolumab), as reflected in the base case. The ITC of Section B.2.9 also demonstrates near-equivalent outcomes between nivolumab-relatlimab and nivolumab + ipilimumab, demonstrating that the long-term outcomes observed for the latter are likely to also be observed for the former.
- There is no direct evidence comparing nivolumab-relatlimab with nivolumab + ipilimumab or pembrolizumab. The relative efficacy of these comparators was informed by a NMA that was conducted following best practice when only aggregate data are available for comparator trials.[125] This approach is, however, inherently more uncertain than a direct comparison. In addition, as PLD were available for both RELATIVITY-047 and CheckMate-067, an ITC was performed. This successfully adjusted for observed differences in patient-level characteristics, with results showing no differences for the common nivolumab comparator. This lends strength to the suggestion that there are no remaining unmeasured confounders influencing the ITC results. As such, this provides strong and compelling evidence in support of using nivolumab + ipilimumab as a reference for informing the expected long-term outcomes for nivolumab-relatlimab
- As no UK-specific clinical data were available for any of the comparators, all efficacy data in the model are taken from global trials. Although these trials are broadly aligned with UK practice, some of the patients in these trials received treatments that are not currently used in the UK

- The magnitude of decrease in HRQL upon progression (0.03) was sourced from the pivotal RELATIVITY-047. Clinical and health economic experts who participated in an advisory board for this appraisal felt that this decrease was too small and may be due to informative censoring. Alternative values from the NICE HEMR (resulting in a decrease of 0.07) were explored in a scenario and found to have a minimal impact on the ICER (Section B.3.10.2).

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A table of variables and inputs used in the base-case analysis along with uncertainty and distributions is provided in Appendix O.

B.3.8.2. Assumptions

Table 67: Base case assumptions

Topic	Assumption	Justification/reason
Perspective and discounting	NHS and PSS payer perspective with costs and QALYs discounted by 3.5% annually	In line with the NICE reference case[83]. (Section B.3.2)
Population	Patient characteristics based on RELATIVITY-047	Considered to be representative of UK clinical practice. (Section B.3.2.1)
Time horizon	Lifetime (40 years)	In line with the NICE reference case[83] (Section B.3.2)
Half-cycle correction	Applied	Section B.3.2
Model structure	Three-state partitioned survival model	Appropriate for an oncology model. Same structure as adopted in NICE Melanoma HEMR.[77] (Section B.3.2.2)
General population mortality	OS and PFS hazards adjusted to ensure they exceed general population hazard of death at all times	Section B.3.3.3
General population utility	Utilities adjusted for age-related decline accounting for gender distribution[108]	Section B.3.4
Treatment duration	IO stopping rule applied at 2 years. Treatment capped at progression	UK clinical validation[37] (Section B.3.3.5)

Topic	Assumption	Justification/reason
Treatment effect waning	Natural waning of relative treatment effect	Hazard function of treatment arms intersect with general population hazards. Assumption strongly supported by long-term data from CheckMate-067 (Section B.3.3.6)
Subsequent treatments	After progression, a proportion of patients are expected to receive further treatment	Distribution and duration of subsequent treatment are guided by the NICE Melanoma HEMR[77] (Section B.3.5.4.1)
Utilities	Health state utilities derived from RELATIVITY-47 applied for all comparators	Captures the impact of disease status.
AE disutilities	Applied per model cycle	Captures impact of different safety profiles between arms. (Section B.3.4.4)
AE costs	Applied per model cycle	Section B.3.5.3
Survival and TTD extrapolations		
Intervention and nivolumab OS	Gompertz	Good visual fit to the observed RELATIVITY-047 KM, smoothed hazards and statistical fit Only model to capture the expected 'plateauing effect' for nivolumab and nivolumab-relatlimab OS, supported by CheckMate-067 long term data, NMA, adjusted ITC and clinical expert opinion at an advisory board (Section B.3.3.3.1)
Nivolumab + ipilimumab OS	Nivolumab + ipilimumab time varying HRs applied to nivolumab reference curve	Best-fitting model (second-order FP) provides a plausible fit to the observed OS data in CheckMate-067 OS curve produced captures expected long-term survivorship and aligns with clinical expert opinion on the expected plateau in OS (Section B.3.3.3.2)
Pembrolizumab OS	Pembrolizumab time varying HRs applied to nivolumab reference curve	Best-fitting model (second-order FP) provides a plausible fit to the observed OS data in KEYNOTE-006 (Section B.3.3.3.3)
Intervention and nivolumab PFS	Piecewise model: KM (first 3 months) + Gompertz	Good visual fit to the observed RELATIVITY-047 KM and smoothed hazards Piecewise approach justified by strong evidence for change in hazards at 3-month in both treatment arms based on visual assessment of observed KM and PFS hazards, further supported by Chow structural change test Only model to appropriately capture the expected 'plateauing effect' for nivolumab and nivolumab-relatlimab PFS, supported by CheckMate-067 long term data, NMA, adjusted ITC and clinical expert opinion at an advisory board (Section B.3.3.4.1)

Topic	Assumption	Justification/reason
Nivolumab + ipilimumab PFS	Nivolumab + ipilimumab time-varying HRs applied to nivolumab reference curve	Best-fitting model (second-order FP) provides a plausible fit to the observed PFS data in CheckMate-067 PFS curve produced captures expected long-term PFS and aligns with clinical expert opinion on the expected plateau in PFS (Section B.3.3.4.2)
Pembrolizumab PFS	Pembrolizumab time-varying HRs applied to nivolumab reference curve	Best-fitting model (second-order FP) provides a plausible fit to the observed OS data in KEYNOTE-006 (Section B.3.3.4.3)
Intervention and nivolumab TTD	Weibull	Chosen based on visual fit, assessment of the hazards and statistical fit assessed by AIC/BIC (Section B.3.3.5)
Nivolumab + ipilimumab TTD	CheckMate-067 KM data	KM data are [redacted]% complete (Section B.3.3.5.2)
Pembrolizumab TTD	Pembrolizumab TTD set equal to nivolumab reference curve	TTD data not readily available from KEYNOTE-006. Clinical experts advised that the TTD for pembrolizumab and nivolumab is highly similar in clinical practice (Section B.3.3.5.3)

B.3.9. Base case results

B.3.9.1. Probabilistic analysis

Probabilistic sensitivity analysis (PSA) was performed to account for joint uncertainties in the key model inputs, in which multiple input parameters were varied simultaneously by sampling their values from uncertainty distributions for 1,000 iterations. Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on parameter variability, a standard error of 10% of the mean was assumed.

B.3.9.1.1. Probabilistic sensitivity analysis results at list prices

The results of the PSA are presented in Table 68 to Table 71. The cost-effectiveness plane is presented in Figure 45. This plots the mean incremental costs and QALYs (relative to nivolumab-relatlimab) from the PSA alongside the deterministic incremental costs and QALYs to highlight the effect of parameter uncertainty on the model results.

Table 68: Mean PSA results, full incremental analysis - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	Incr. ICER
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,215
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£148,869
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.							

Table 69: Mean PSA pairwise results nivolumab-relatlimab versus nivolumab - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£87,582
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 70: Mean PSA pairwise results - nivolumab-relatlimab versus nivolumab + ipilimumab - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£148,869
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 71: Mean PSA pairwise results - nivolumab-relatlimab versus pembrolizumab - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER

Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,670
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA with list prices is shown in Figure 45. The willingness-to-pay threshold presented in this figure represents a willingness-to-pay threshold of £30,000 per QALY gained.

Figure 45: Cost effectiveness plane relative to nivolumab-relatlimab - list prices

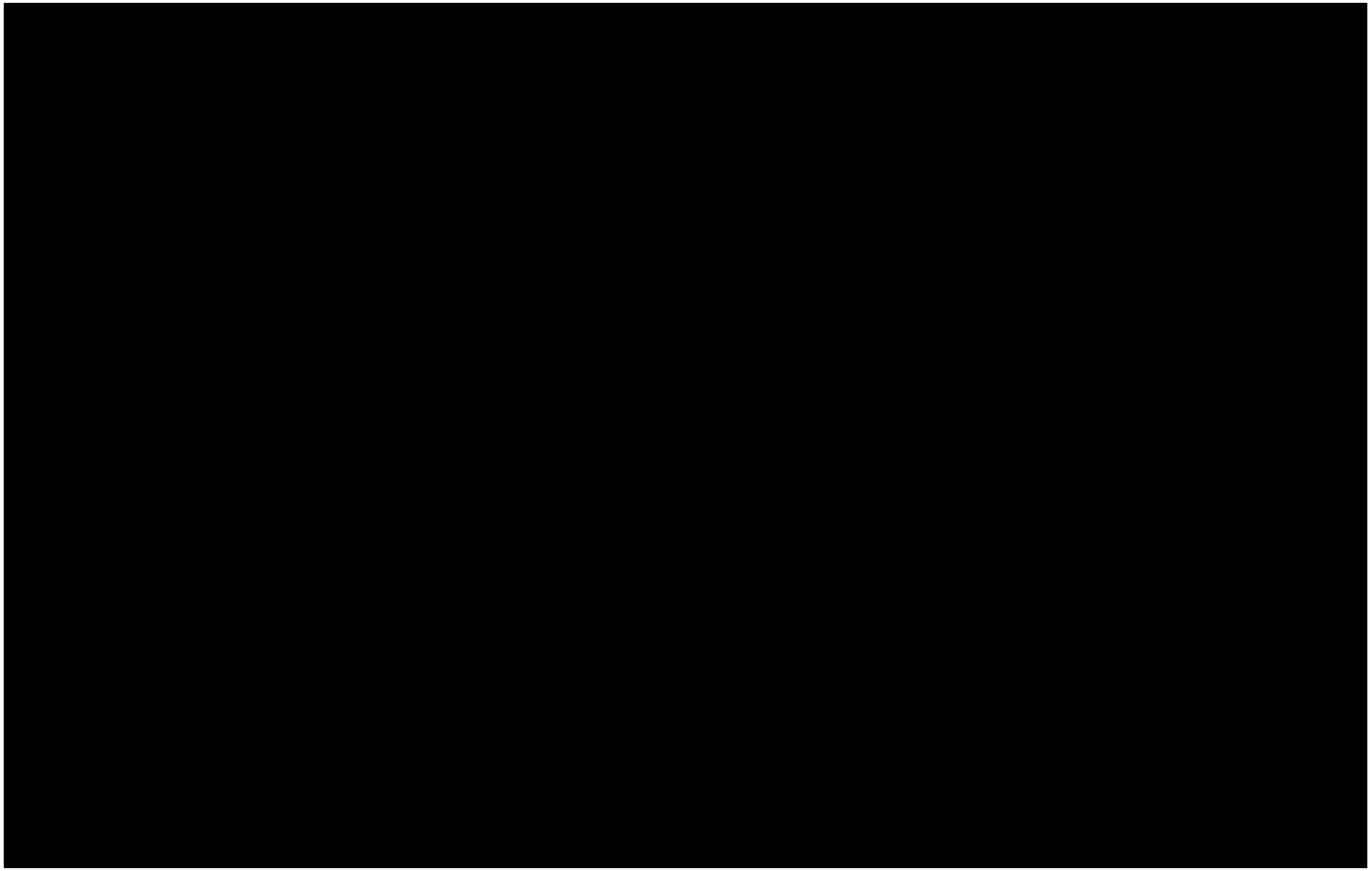

Figure 46 presents the cost-effectiveness acceptability curve, showing the likelihood of each comparator being the most cost-effective at different willingness-to-pay thresholds.

Figure 46: Cost-effectiveness acceptability curve (CEAC) - list prices

B.3.9.1.2. Probabilistic sensitivity analysis results incorporating confidential discounts

Results of the probabilistic sensitivity analysis incorporating confidential discounts for nivolumab, nivolumab-relatlimab, and nivolumab + ipilimumab are presented in Table 72 to Table 75 (the magnitude of discount for pembrolizumab is unknown so not included).

Table 72: Mean PSA results, full incremental analysis – PAS prices for all BMS assets, pembrolizumab at list price

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	Incr. ICER
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,329
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.							

Table 73: Mean PSA pairwise results nivolumab-relatlimab versus nivolumab – PAS prices for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]	[redacted]	[redacted]	–	–	–	–
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,329
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 74: Mean PSA pairwise results - nivolumab-relatlimab versus nivolumab + ipilimumab – PAS prices for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	–	–	–	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 75: Mean PSA pairwise results - nivolumab-relatlimab versus pembrolizumab – PAS prices for all BMS assets, pembrolizumab at list price

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER

Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA with PAS prices incorporated for all BMS assets is shown in Figure 47. The willingness-to-pay threshold presented in this figure represents a threshold of £30,000 per QALY gained.

Figure 47: Cost-effectiveness plane incorporating confidential discounts for all BMS assets, pembrolizumab at list price

Figure 48 presents cost-effectiveness acceptability curves for each model arm, showing the likelihood of each comparator being the most cost-effective at different willingness-to-pay thresholds when confidential discounts for all BMS assets are incorporated.

Figure 48: Cost-effectiveness acceptability curves (CEAC) - PAS prices for all BMS assets, pembrolizumab at list price

B.3.9.2. Base case deterministic incremental cost-effectiveness analysis results

B.3.9.2.1. Base case deterministic results at list prices

Fully incremental base case results at list prices are presented in Table 76. Disaggregated results are available in Appendix J. Results of the pairwise analysis against all comparators are presented in Table 77 to Table 79.

Table 76: Base-case results – List prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,395
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£133,373

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.

Table 77: Base-case pairwise results nivolumab-relatlimab versus nivolumab monotherapy – List prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]	[redacted]	[redacted]				
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£88,991

Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.

Table 78: Base-case pairwise results – nivolumab-relatlimab versus nivolumab + ipilimumab – List prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]				
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£133,373

Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.

Table 79: Base-case pairwise results – nivolumab-relatlimab versus pembrolizumab – List prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,415
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

B.3.9.2.2. Base case deterministic results incorporating confidential discounts

The full incremental cost-effectiveness results with prices incorporating confidential discounts for all BMS assets are presented in Table 80. Pairwise analyses are presented with confidential discounts included for all BMS assets in Table 81 to Table 83.

Table 80: Base-case results – with PAS for all BMS assets, pembrolizumab at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,519
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 81: Base-case pairwise results nivolumab-relatlimab versus nivolumab monotherapy – with PAS for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,519
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 82: Base-case pairwise results - nivolumab-relatlimab versus nivolumab + ipilimumab – with PAS for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 83: Base-case pairwise results - nivolumab-relatlimab versus pembrolizumab – with PAS for all BMS assets, pembrolizumab at list price

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

B.3.10. Exploring uncertainty

B.3.10.1. Deterministic sensitivity analysis

For one-way sensitivity analysis (OWSA), values for all parameters with univariate uncertainty distributions were set to their upper and lower limits reported in Appendix O.

B.3.10.1.1. Deterministic sensitivity analysis results at list prices

Figure 49 to Figure 51 present the results of the OWSA in the form of tornado diagrams. Each figure shows the 10 parameters with the most influence on the ICER for each pairwise comparison with nivolumab-relatlimab. Health state utilities and inputs used to calculate the cost of health care resource use in the model are among the most influential for each comparator. For the comparison against nivolumab + ipilimumab, the incidence and cost of treating colitis are in the 10 most influential parameters, whilst no AE inputs feature in the most influential parameters for the ICER against nivolumab or pembrolizumab. This reflects the relative safety profile of nivolumab + ipilimumab compared to other modelled regimens.

Figure 49: Deterministic sensitivity analysis tornado diagram, versus nivolumab – list prices

Figure 50: Deterministic sensitivity analysis tornado diagram, versus nivolumab + ipilimumab – list prices

Figure 51: Deterministic sensitivity analysis tornado diagram, versus pembrolizumab – list prices

B.3.10.1.2. Deterministic sensitivity analysis results incorporating confidential discounts

The results of the OWSA with PAS discounts incorporated for all BMS assets are presented in Figure 52 to Figure 54 as tornado diagrams showing the 10 parameters with the most influence on the ICER against each comparator. In each comparison health state utility values, and the inputs used to calculated the cost of health care

resource use are among the most influential parameters. As with the list price OWSA, in the comparison against nivolumab + ipilimumab, the cost and incidence of colitis are amongst the most influential parameters.

Figure 52: Deterministic sensitivity analysis tornado diagram, versus nivolumab – PAS prices

Figure 53: Deterministic sensitivity analysis tornado diagram, versus nivolumab + ipilimumab – PAS prices for all BMS assets

Figure 54: Deterministic sensitivity analysis tornado diagram, versus pembrolizumab – PAS prices for all BMS assets, pembrolizumab at list price

B.3.10.2. Scenario analysis

To test the sensitivity of the model to changing one or more model inputs or structural assumptions, a number of scenarios were tested.

B.3.10.2.1. Scenario analysis results – list prices

Table 84 describes the scenarios tested and presents the impact on the ICER with all modelled treatments at list price. The most impactful scenarios across all comparisons are the application of stopping rules for all treatment arms at 5 years rather than 2 years in the base case; the choice of model used to extrapolate nivolumab-relatlimab; the source of health state utility values; and not capping TTD by PFS. Figure 55 to Figure 57 graphically show the most influential scenarios on the ICER for each pairwise comparator.

Figure 55: Scenario analysis tornado diagram versus nivolumab - list prices

Figure 56: Scenario analysis tornado diagram versus nivolumab + ipilimumab - list prices

Figure 57: Scenario analysis tornado diagram versus pembrolizumab - list prices

Table 84: Scenario analysis – List prices

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
	Base case		£88,991	£133,373	£40,415
1	1.5% discounting		[redacted]	[redacted]	[redacted]
2	NICE Melanoma HEMR health state utilities	Alternative source of utilities. (Section B.3.4.5)	[redacted]	[redacted]	[redacted]
3	No-age adjustment to utilities	Explore the impact of age-related utility adjustment. (Section B.3.4.5)	[redacted]	[redacted]	[redacted]
4	Stopping rules applied at 5 years	Available evidence suggests some treatment occurs beyond official stopping rules. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
5	10% of patients continue/reinitiate IO treatment after 2 years	UK clinical validation[37] (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
6	Pembrolizumab TTE equal to nivolumab	UK clinical validation[37] (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
7	Nivolumab-relatlimab and nivolumab OS generalized gamma	Lack of long-term data for nivolumab-relatlimab survival outcomes. Settings also applied to nivolumab for consistency. Next most plausible extrapolating model. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
8	Nivolumab-relatlimab and nivolumab PFS 1 knot odds spline model		[redacted]	[redacted]	[redacted]

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
9	Time horizon 30 years		[redacted]	[redacted]	[redacted]
10	TTD not capped by PFS	To explore potential treatment beyond progression. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
11	Nivolumab-relatlimab TTD gamma model	Lack of long-term data for nivolumab-relatlimab TTD. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
12	Nivolumab CheckMate-067 KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
13	Pembrolizumab SACT KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
14	Nivolumab-relatlimab subsequent treatment proportion equal to nivolumab	Alternative assumption on subsequent treatment proportion (Section B.3.5.4.1)	[redacted]	[redacted]	[redacted]
15	Reduction in subsequent treatment proportions by 20% (all treatment arms)	Alternative assumption on subsequent treatment proportions (Section B.3.5.4.1)	[redacted]	[redacted]	[redacted]

Key: HEMR, health economic modelling report; IO, immune-oncology; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy database; TTD, time to treatment discontinuation; TTE, time to event.

B.3.10.2.2. Scenario analysis results – incorporating confidential discounts

Table 85 describes the scenarios tested and presents the impact on the ICER with confidential discounts incorporated for all BMS assets. In the comparisons with nivolumab and nivolumab + ipilimumab the most influential scenarios are the application of a stopping rule for all model arms at 5 years rather than 2 years; the choice of nivolumab-relatlimab TTE extrapolations; and setting discount rates to 1.5%. The most impactful scenarios in the comparison to pembrolizumab are the variation of confidential discounts applied to pembrolizumab. Figure 58 to Figure 60 graphically show the most influential scenarios on the ICER for each pairwise comparator.

Figure 58: Scenario analysis tornado diagram versus nivolumab – PAS prices for all BMS assets

Figure 59: Scenario analysis tornado diagram versus nivolumab + ipilimumab – PAS prices for all BMS assets

Figure 60: Scenario analysis tornado diagram versus pembrolizumab – PAS prices for all BMS assets, pembrolizumab at list price

Table 85: Scenario analysis – incorporating confidential discounts for all BMS assets, pembrolizumab at list price

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
	Base case		£27,519	Nivolumab-relatlimab dominates	Nivolumab-relatlimab dominates
1	1.5% discounting		[redacted]	[redacted]	[redacted]
2	NICE Melanoma HEMR health state utilities	Alternative source of utilities. (Section B.3.4.5)	[redacted]	[redacted]	[redacted]
3	No-age adjustment to utilities	Explore the impact of age-related utility adjustment. (Section B.3.4.5)	[redacted]	[redacted]	[redacted]
4	Stopping rules applied at 5 years	Available evidence suggests some treatment occurs beyond official stopping rules. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
5	10% of patients continue/reinitiate IO treatment after 2 years	UK clinical validation[37] (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
6	Pembrolizumab TTE equal to nivolumab	UK clinical validation[37] (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
7	Nivolumab-relatlimab and nivolumab OS generalized gamma	Lack of long-term data for nivolumab-relatlimab survival outcomes. Settings also applied to nivolumab for consistency. Next most plausible extrapolating model. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
8	Nivolumab-relatlimab and nivolumab PFS 1 knot odds spline model		[redacted]	[redacted]	[redacted]

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
9	Time horizon 30 years		[redacted]	[redacted]	[redacted]
10	TTD not capped by PFS	To explore potential treatment beyond progression. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
11	Nivolumab-relatlimab standard gamma model (TTD)	Lack of long-term data for nivolumab-relatlimab TTD. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
12	Nivolumab CheckMate-067 KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
13	Pembrolizumab SACT KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
14	Nivolumab-relatlimab subsequent treatment proportion equal to nivolumab	Alternative assumption on subsequent treatment proportion (Section B.3.5.4.1)	[redacted]	[redacted]	[redacted]
15	Reduction in subsequent treatment proportions by 20% (all treatment arms)	Alternative assumption on subsequent treatment proportions (Section B.3.5.4.1)	[redacted]	[redacted]	[redacted]
16	Pembrolizumab discount set to 0%	The discount applied to pembrolizumab is unknown	[redacted]	[redacted]	[redacted]
17	Pembrolizumab discount set to 45%		[redacted]	[redacted]	[redacted]
18	Pembrolizumab discount set to 50%		[redacted]	[redacted]	[redacted]

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
19	Pembrolizumab discount set to 55%		[redacted]	[redacted]	[redacted]
20	Pembrolizumab discount set to 60%		[redacted]	[redacted]	[redacted]
21	Pembrolizumab discount set to 65%		[redacted]	[redacted]	[redacted]
22	Pembrolizumab discount set to 70%		[redacted]	[redacted]	[redacted]
23	Pembrolizumab discount set to 75%		[redacted]	[redacted]	[redacted]
24	Pembrolizumab discount set to 80%		[redacted]	[redacted]	[redacted]
25	Pembrolizumab discount set to 85%		[redacted]	[redacted]	[redacted]
26	Pembrolizumab discount set to 90%		[redacted]	[redacted]	[redacted]
27	Pembrolizumab discount set to 100%		[redacted]	[redacted]	[redacted]
28	Pembrolizumab discount set to 95%		[redacted]	[redacted]	[redacted]
29	Pembrolizumab discount set to 5%		[redacted]	[redacted]	[redacted]
30	Pembrolizumab discount set to 10%		[redacted]	[redacted]	[redacted]

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
31	Pembrolizumab discount set to 15%		[redacted]	[redacted]	[redacted]
32	Pembrolizumab discount set to 20%		[redacted]	[redacted]	[redacted]
33	Pembrolizumab discount set to 25%		[redacted]	[redacted]	[redacted]
34	Pembrolizumab discount set to 30%		[redacted]	[redacted]	[redacted]
35	Pembrolizumab discount set to 35%		[redacted]	[redacted]	[redacted]
36	Pembrolizumab discount set to 40%		[redacted]	[redacted]	[redacted]

Key: HEMR, health economic modelling report; IO, immune-oncology; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy database; TTD, time to treatment discontinuation; TTE, time to event.

B.3.11. Subgroup analysis

No subgroups are considered in the cost-effectiveness analysis.

B.3.12. Benefits not captured in the QALY calculation

The use of nivolumab-relatlimab may result in potential HRQL benefits in patients' caregivers that are unlikely to be included in the QALY calculation. In addition, as the AEs included in the economic model were those Grade 3+ which occurred in at least 1% of patients in any treatment arm there are some AEs excluded from the analysis. It was noted by clinicians that for some patients there may be a substantial impact on HRQL from the cumulative impact of many Grade 1 or Grade 2 AEs. [37] This is particularly relevant when considering the benefits of nivolumab-relatlimab when compared to nivolumab + ipilimumab which has a notably worse safety profile.[104]

B.3.13. Validation

B.3.13.1. Validation of cost-effectiveness analysis

Expert input was sought during the development of the cost-effectiveness analysis. An advisory board of both clinical and health economic experts was conducted whereby model inputs and assumptions were validated.[37] This ensured that the inputs and assumptions used in the base-case analysis were relevant to UK clinical practice to validate the clinical plausibility of the predicted outcomes.

The cost-effectiveness model was developed in line with the NICE reference case and NICE's melanoma HEMR.[77, 83] A quality control check was conducted using a checklist developed using publicly available checklists, such as Drummond and Philips, as a guide.[126] The checklist includes all checks listed in the TechVER checklist.[127] The quality control check was led by an experienced, unconflicted health economist who had not been involved in the development of the original model.

Estimates from both the health economic model and the NMA were also compared with estimates from clinical trials, to ensure they generate plausible predictions (Appendix O).

B.3.14. Interpretation and conclusions of economic evidence

The economic SLR identified no previous economic evaluations of nivolumab-relatlimab for the treatment of untreated, unresectable or metastatic melanoma. Therefore, a de novo economic model was developed to support this submission. The economic analysis drew relevant inputs from the pivotal RELATIVITY-047 trial, previous appraisals of therapies in this indication, and published literature where possible. The economic evaluation compares health outcomes for patients treated with nivolumab-relatlimab with those of patients treated with relevant comparators.

The economic analysis compares nivolumab-relatlimab with nivolumab, nivolumab + ipilimumab and pembrolizumab using patient-level data from RELATIVITY-047, and an NMA to derive relative treatment effects from CheckMate-067 and KEYNOTE-006. A range of analyses based on time-to-event data for OS, PFS and TTD were conducted according to best practice guidance to model health outcomes over a lifetime horizon. The approaches were assessed for robustness and appropriateness for use in the economic model based on NICE DSU TSD guidance. The base case analysis used the most clinically valid and best fitting survival models, with plausible alternative models tested in scenarios as presented in Section B.3.10.2. However, all survival models were considered to underestimate the true lifetime benefit of nivolumab-relatlimab.

With all treatments at list prices, the mean probabilistic ICER for nivolumab-relatlimab vs nivolumab is £87,582 per QALY gained, £148,869 versus nivolumab + ipilimumab, £43,670 versus pembrolizumab. The mean probabilistic results also show that nivolumab-relatlimab is associated with an incremental health benefit compared with all comparator regimens, offering an additional [redacted] LYs and [redacted] QALYs against nivolumab, [redacted] LYs and [redacted] QALYs compared to nivolumab + ipilimumab, [redacted] LYs and [redacted] QALYs compared to pembrolizumab.
Results are also presented incorporating the PAS currently agreed for all BMS assets included in the analysis. These results show that nivolumab-relatlimab is highly likely to dominate both nivolumab + ipilimumab and pembrolizumab, whilst having an ICER below £30,000 per QALY versus nivolumab when confidential

discounts are included. Deterministic base case results are consistent with the mean probabilistic results. The deterministic base case ICERs were £[redacted] per QALY gained against nivolumab, £[redacted] against nivolumab + ipilimumab, £[redacted] against pembrolizumab.

There is some uncertainty relating to the extrapolation of long-term OS and PFS. All the survival models explored underestimated the expected benefit of nivolumab-relatlimab over a lifetime horizon when compared with long-term external evidence. The nivolumab-relatlimab cost-effectiveness results should hence be considered a conservative estimate for decision making. The choice of TTE extrapolations for nivolumab-relatlimab are shown in scenario analyses (Section B.3.10.2) to be influential for all modelled ICERs. Additionally, the confidential discount for pembrolizumab is unknown, therefore cost-effectiveness results are sensitive to the PAS discount included for pembrolizumab.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection, and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality -of -life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: American Joint Committee on Cancer Staging System

Appendix N: Additional information for RELATIVITY-047

Appendix O: Additional cost-effectiveness information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Summary of Information for Patients (SIP)

April 2023

File name	Version	Contains confidential information	Date
ID1688_Opdualag_ STA_SIP_21072023	V4.0	No	21st July 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Nivolumab-relatlimab (Opdualag®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Nivolumab-relatlimab will be used for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The application for market authorisation with the UK Medicines and Healthcare products Regulatory Agency (MHRA) is currently ongoing. Approval is expected and current anticipated dates can be found in Table 2 of Document B.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Financial support has been provided to the following patient groups: • Melanoma Focus – Sponsorship of virtual regional meeting (2023) – £6,000.00 – A grant to support the 2023 UK Melanoma Patient Conference (2023) – £6,000.00

- Sponsorship of 2022 virtual regional meeting (2022) – £6,000.00
- Support for melanoma awareness campaign (2022) – £10,000.00
- Sponsorship of 2022 Focus on Melanoma meeting (2022) – £10,000.00

- Melanoma UK
  - Sponsorship melanoma UK skin health campaign (2022) – £60,000.00
- Melanoma Fund
  - Grant donation (2023) – £7,000.00
  - Grant donation (2022) – £13,500.00

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Melanoma is a form of skin cancer that develops in skin cells called melanocytes. Melanocytes produce melanin, a skin-darkening pigment that gives skin its natural colour whilst helping to protect the body from ultraviolet (UV) light.[1] Melanoma is much less common than some other types of skin cancer. However, compared with these other skin cancers, it is much more likely to spread to other parts of the body if it is not caught and treated early.

Melanoma is the fifth most common type of cancer in the UK, accounting for 4% of all new cancer cases.[2] Between 2013 and 2017, 62,656 cases of melanoma were diagnosed in adults (aged 15–99) in England. Of these 62,565 cases, 5,199 (8.3%) were diagnosed at Stage III or IV.[3] This equates to approximately 1,040 Stage III or IV melanoma cases diagnosed in England each year.

While it is in the early stages (i.e. Stage I, II and III), melanoma is asymptomatic (meaning that it does not show any symptoms) and can be treated successfully through surgery to remove the melanoma and a small area of skin around it.[4] However, if undetected, melanoma can spread to other parts of the body; this is referred to as metastatic melanoma (Stage IV). The typical symptoms of metastatic melanoma can include pain, fatigue, weight loss, loss of appetite, nausea and shortness of breath.[5] As well as physical symptoms, approximately one-third of patients with melanoma experience high levels of distress, mostly at the time of diagnosis and following treatment.[6]

Metastatic melanoma also places a high financial burden on patients and society. In fact, melanoma has the highest loss of economic productivity cost in Europe compared with other cancers.[7] This is due to the fact that over 25% of skin cancer cases are diagnosed in people under the age of 50 years; this is unusually early compared with other types of cancer, meaning patients are more likely to be economically active and/or in full-time employment.[4]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Melanoma can look different from person to person. The first visible sign of a melanoma is often a new mole, or a change in appearance of an existing mole.[8] The ABCDE checklist, as presented in Table 1, provides a list of possible signs of melanoma. This list is not definitive, and it should only be used as a starting point.[9] If melanoma is suspected, patients will be referred to a dermatology clinic where the mole and the rest of the skin is examined. The mole may be removed and sent for biopsy.

Table 1: The ABCDE checklist

A	Asymmetry
B	Border: irregular, ragged, notched, or blurred edges
C	Colour: non-uniform
D	Diameter: larger than 6 mm
E	Evolving: changing in size, shape or colour

Source: Sundarajan et al., 2021.[8]

If a patient is already being treated for melanoma, they may still be going to clinics for check-ups. During these check-ups, metastatic melanoma can sometimes be found. In rare cases, a person may be diagnosed with advanced melanoma without having found the original melanoma on the skin.[5] Symptoms of advanced melanoma can begin years after the original melanoma was removed, whereas for others, the melanoma may be advanced when it is first diagnosed.

No additional diagnostic tests are required before starting treatment with nivolumab-relatlimab.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - If there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The most recent guidelines for the treatment of untreated unresectable or metastatic melanoma in the UK are the NICE melanoma assessment and management guidelines (NG14, 2022).[10] These guidelines recommend the first-line treatment of immunotherapy. Clinicians should consider the following factors when deciding on a patient's most appropriate treatment:

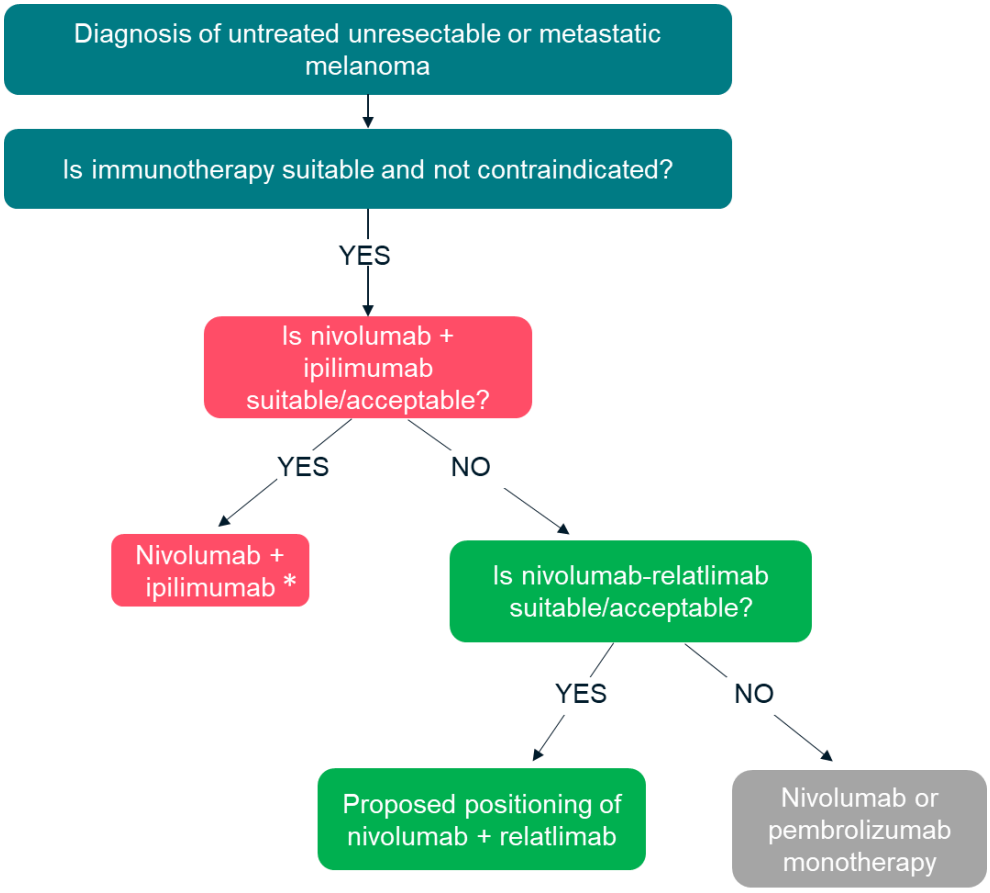
- Whether there are any comorbidities (i.e. when a person has more than one disease or condition at the same time)
- A patient's performance status (measured according to the Eastern Cooperative Oncology Group)

- The risk of treatment toxicity
- Whether potential treatment toxicity will be tolerated
- The presence of symptomatic brain metastases

Figure 1 presents the clinical pathway of care for patients with untreated unresectable or metastatic melanoma, and the proposed positioning of nivolumab-relatlimab in the pathway. The NICE guidelines recommend nivolumab + ipilimumab as the primary choice of immunotherapy treatment. When treatment with nivolumab + ipilimumab is unsuitable or unacceptable (e.g. due to potential side effects of the treatment), pembrolizumab or nivolumab monotherapy should be offered. While the NICE guidelines recommend nivolumab + ipilimumab as the primary choice immunotherapy treatment, UK clinicians have expressed the opinion that the choice of treatment depends on the patient's suitability to treatment.[11]

UK clinicians have confirmed that the vast majority of patients with advanced melanoma are receiving treatment with nivolumab + ipilimumab, and the remainder of patients are being treated with an immuno-oncology monotherapy, mainly pembrolizumab.

Figure 1: Clinical pathway of care for patients with untreated unresectable or metastatic melanoma and the proposed positioning of nivolumab-relatlimab



Notes: * Clinicians noted that nivolumab-relatlimab may be a good alternative for some patients who are currently considered unfit for receive nivolumab + ipilimumab, or in centres without the capacity or experience to manage potential toxicities that arise from treatment with nivolumab + ipilimumab.
Source: Adapted from the NICE melanoma guidelines (2022)[10]

There are currently no known drug–drug interactions and/or contraindications that commonly cause challenges for patients with untreated unresectable or metastatic melanoma.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

A systematic literature review (SLR) was performed in 2008 to collect all the available evidence on how melanoma treatment affects the quality of life of patients with advanced melanoma. The study concluded that at initial diagnosis, patients were found to have a high level of functioning, meaning the disruption to their quality of life was minimal. However, as the disease progresses, patients begin to decline in almost all of the major functional areas, aligning with an increase in symptoms of their disease and the side effects of the therapies used to treat the illness.[12]

Since this review was conducted, new immunotherapy treatment options (e.g. nivolumab + ipilimumab, nivolumab monotherapy) have been introduced to the treatment landscape. The CheckMate 067 trial demonstrated that treatment with nivolumab + ipilimumab and nivolumab monotherapy both maintained the quality of life of patients from the start of treatment to the last follow-up visit at Week 79.[13]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Nivolumab and relatlimab are both immune checkpoints inhibitors. This type of treatment blocks proteins that stop the immune system from attacking the cancer cells.

How do immune checkpoint inhibitors work?

There are many different types of immune cells in the body. One type of immune cell, the T-cell, plays a key role in fighting infection, as well as in detecting and attacking cancer cells.

T-cells have certain proteins on their surface that turn the immune system on when the cells are needed to fight foreign bodies, and other proteins that turn the immune system off when an immune response is no longer needed.[14] These proteins are known as checkpoint proteins. However, cancer cells are often able to turn off T-cells, thereby stopping them from recognising and attacking the cancer cells.

One class of drugs, called immune checkpoint inhibitors, work by blocking the ability of cancer cells to 'turn off' the T-cells. In this way, they can restore the natural ability of T-cells to recognise and attack cancer cells.[14] And because they work through enhancing the immune system, they are known as immune-oncology therapies.

Nivolumab blocks an immune checkpoint protein called PD-1, whereas relatlimab is a new drug that blocks a different immune checkpoint protein called LAG-3.[15] Relatlimab is the first checkpoint inhibitor proven to be effective at targeting LAG-3, making nivolumab-relatlimab a novel combination immuno-oncology treatment in the melanoma pathway.[16]

A link to the FDA prescribing information leaflet is provided below:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761234s000lbl.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

The medicine is not intended to be used in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Method of administration – Nivolumab-relatlimab is administered as an intravenous (IV) infusion over 30 minutes. An IV infusion is a way of delivering medicine directly into the bloodstream. Nivolumab-relatlimab is given to patients every 4 weeks until the disease progresses, or until the patient experiences side effects that are intolerable.

Dosage – Nivolumab-relatlimab is the first fixed-dose combination immuno-oncology treatment, meaning nivolumab and relatlimab are two drugs that are combined into a single dose. For adult patients and paediatric patients aged 12 years or older who weigh at least 30 kg, the recommended dosage of nivolumab-relatlimab is 480 mg nivolumab and 160 mg relatlimab.[17] Reducing the dose of nivolumab-relatlimab once the treatment has started is not recommended. The recommended dosage for paediatric patients 12 years of age or older who weigh less than 40 kg has not yet been established.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

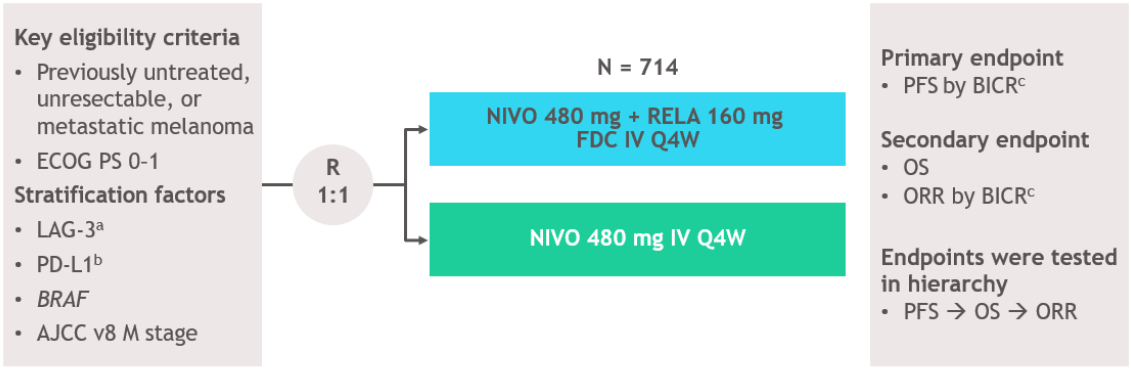
Nivolumab-relatlimab has been studied in the RELATIVITY-047 trial, the first large clinical study to show that targeting both LAG-3 and PD-1 can be an effective approach for treating patients with advanced melanoma.[16]

RELATIVITY-047 is an ongoing, international, Phase 2/3 trial in which patients were randomised to receive either nivolumab-relatlimab or nivolumab monotherapy as an initial, or first-line treatment for advanced melanoma.[16]

Figure 2 presents the design of the RELATIVITY-047 trial. The trial included more than 700 patients from over 20 different countries, including the UK.[16] To be included in the trial, patients had to match the following criteria:

- ≥ 12 years of age
- Have a confirmed diagnosis of Stage III (unresectable) or Stage IV melanoma
- Have not received prior systemic anti-cancer treatment for unresectable or metastatic melanoma*
- Have an Eastern Cooperative Oncology Group performance status of 0 or 1 (i.e. patients who have no symptoms or are symptomatic but able to walk/not confined to bedrest)

Figure 2: RELATIVITY-047 trial design



Key: AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; FDC, fixed dose combination; IV, intravenous; LAG-3, lymphocyte-activation gene-3; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q4W, every 4 weeks; R, randomised.
Source: Long et al., 2022.[18]

Further information/publications for RELATIVITY-047:

Clinicaltrials.gov (NCT03470922[19]) – https://clinicaltrials.gov/ct2/show/NCT03470922
Publication (Tawbi et al. 2022[16]) – – https://www.nejm.org/doi/full/10.1056/nejmoa2109970

*Patients were still eligible for enrolment if they had previously received treatment for melanoma, usually after surgery to reduce the risk of melanoma returning and spreading.[16, 20]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

RELATIVITY-047 is the first large clinical trial to demonstrate that targeting both PD-1 and LAG-3 can be effective at treating patients with advanced melanoma. As summarised in Q3d), patients in this trial received either nivolumab-relatlimab or nivolumab monotherapy as an initial, or first-line treatment for advanced melanoma.[16]

Several database locks have been conducted during the RELATIVITY-047 trial. are presented below. All RELATIVITY-047 data presented in this document are from the October 2021 database lock (median follow-up: 19.3 months), as presented at 2022 American Society of Clinical Oncology (ASCO) conference.[18] Data from the most recent October 2022 database lock are confidential; please refer to Document B of the company submission for October 2022 from the RELATIVITY-047 trial.

Primary endpoint: progression-free survival

The primary endpoint of the trial was progression-free survival, meaning the length of time between starting the treatment and the appearance of any signs that the melanoma has started to grow again.[21]

Table 2 presents a summary of the progression-free survival results from the RELATIVITY-047 trial. The median progression-free survival was 10.2 months with nivolumab-relatlimab, compared with 4.6 months for patients receiving nivolumab.[18] The percentage of patients who had not progressed by 12 months was 48% with nivolumab-relatlimab, compared with 37% of patients receiving nivolumab monotherapy.

Table 2: Analysis of PFS in the RELATIVITY-047

	Nivolumab-relatlimab (n = 355)	**Nivolumab (n = 359)**
Median PFS	10.2 months	4.6 months
The percentage of patients in which the disease had not progressed at:		
12 months	48%	37%
24 months	39%	29%

Key: PFS, progression-free survival.
Source: Long et al. 2022[18]

Secondary endpoint: overall survival

One of the secondary endpoints of the RELATIVITY-047 trial was overall survival, meaning how long the patients lived after starting treatment. The median overall survival was not reached in the nivolumab-relatlimab arm[18]; this means researchers could not calculate a median survival because more than half of the patients in the study were still living. The median overall survival in the nivolumab monotherapy arm was 34.1 months. Over a median trial follow-up of 19.3 months, 137 (38.6%) patients had died in the nivolumab-relatlimab arm and 160 (44.6%) patients had died in the nivolumab arm.[18]

Secondary endpoint: objective response rate

Table 3 presents the definitions of the terms complete response (CR), partial response (PR) and overall response rate (ORR). Patients treated with nivolumab-relatlimab experienced an improvement in the ORR compared with patients treated with nivolumab monotherapy. Among the patients who received nivolumab-relatlimab, the confirmed ORR was 43.1%; of these, 58 (16.3%) patients achieved a CR and 95 (26.8%) achieved a PR.[18] For the nivolumab monotherapy arm of the trial, the ORR was 32.6%; of these, 51 (14.2%) patients achieved a CR and 66 (18.4%) patients achieved a PR.[18]

Table 3: Outcome definitions

Term	Definition
Complete response (CR)	There are no signs of cancer on scans or tests.
Partial response (PR)	The cancer has shrunk by at least one third (30%), and there are no signs the cancer has grown anywhere else in the body.
Overall response rate (ORR)	The total number of people whose cancer has either gone away (a complete response) or shrunk (a partial response).
Source: Cancer Research UK, 2022[21]	

Comparison of efficacy for nivolumab-relatlimab versus nivolumab + ipilimumab, nivolumab-relatlimab versus pembrolizumab and nivolumab-relatlimab versus nivolumab

Two comparisons have been performed to compare the efficacy of treatments for untreated unresectable metastatic melanoma: a network meta-analysis and an adjusted indirect treatment comparison.

A network meta-analysis compares three or more treatments simultaneously in a single analysis by combining evidence from several studies. This provides a way to compare the efficacy of treatments, even though they were not studied together in a single trial. In this analysis, nivolumab-relatlimab is compared with nivolumab + ipilimumab, pembrolizumab and nivolumab.

The results of the network meta-analysis suggest that, among adults with previously untreated unresectable or metastatic melanoma:

- Nivolumab-relatlimab performs similarly to nivolumab + ipilimumab in terms of progression-free survival and overall survival
- Nivolumab-relatlimab performs better than both nivolumab and pembrolizumab in terms of overall survival and progression-free survival

A comparison of nivolumab-relatlimab and nivolumab + ipilimumab was also performed via an adjusted indirect treatment comparison. Unlike a network meta-analysis, an adjusted indirect treatment comparison tends to compare the relative results of two treatments. For this analysis specifically, BMS have access to patient-level data from their two trials RELATIVITY-047 and CheckMate-067. This provides information on individual people, including information on demographic characteristics (such as age and gender), comorbidities, treatment history and medical history.

The results of the adjusted indirect treatment comparison align with the results from the network meta-analysis, suggesting that nivolumab-relatlimab performs similarly to nivolumab + ipilimumab in terms of progression-free survival and overall survival in patients with previously untreated unresectable or metastatic melanoma.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The RELATIVITY-047 trial evaluated the health-related quality of life (HRQL) of patients who received treatment. The latest HRQL data are from the March 2021 database lock, as presented in Schadendorf et al. 2021.[22] HRQL was evaluated prior to dosing in each 4-week treatment cycle using the Functional Assessment of Cancer Therapy-melanoma (FACT-M) questionnaire and the EQ-5D-3L questionnaire.[23, 24] The FACT-M questionnaire includes the four FACT-general (FACT-G) subscales of physical, social/family, emotional, and functional well-being, in addition to the FACT-M melanoma subscale and a melanoma surgery scale.[24]

The proportion of patients completing the questionnaire at each treatment visit was ≥ 86%.[22] Both the EQ-5D-3L and FACT-M questionnaires showed that the least-squares (LS) mean change from baseline was similar in the nivolumab-relatlimab and nivolumab monotherapy arms of the trial, meaning nivolumab-relatlimab does not cause further detriment to the patient's quality of life.[22]

For more information regarding the burden of advanced melanoma on the quality of life of patients, please refer to Question 2d.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Please note, all RELATIVITY-047 data presented in this document are from the October 2021 database lock (median follow-up: 19.3 months), as presented at 2022 American Society of Clinical Oncology (ASCO) conference.[18] Data from the most recent October 2022 database lock are confidential; please refer to Document B of the company submission for October 2022 from the RELATIVITY-047 trial.

The adverse events associated with treatment with nivolumab-relatlimab were generally manageable. The type and rate at which adverse events occurred for patients receiving nivolumab-relatlimab was similar as for patients treated with other checkpoint inhibitors. No new safety signals or events were identified when compared with nivolumab monotherapy.[18] Adverse events were also less common for nivolumab-relatlimab than for other immunotherapy combinations such as nivolumab + ipilimumab, as confirmed by the network meta-analysis and adjusted indirect treatment comparison introduced in Question 3e.

The frequency and severity of all-cause and drug-related adverse events, serious adverse events, and adverse events leading to discontinuation were generally higher in the nivolumab-relatlimab arm compared with the nivolumab monotherapy arm.[18] Treatment-related side effects were experienced by 297 (83.7%) patients in the nivolumab-relatlimab arm and 260 (72.4%) patients in the nivolumab arm.[18] The occurrence of treatment-related adverse events led 15.2% of the patients in the nivolumab-relatlimab arm of the trial to stop treatment, compared with 7.2% of patients in the nivolumab monotherapy group.[18]

Table 4 presents the most commonly reported adverse events in the RELATIVITY-047 trial. The type of adverse events experienced were similar between the treatment arms.

Table 4: Frequently reported treatment-related adverse events

	Nivolumab-relatlimab (n = 355)		Nivolumab (n = 359)	
	Any Grade	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Pruritus	87 (24.5)	0 (0.0)	59 (16.4)	2 (0.6)
Fatigue	83 (23.4)	5 (1.4)	47 (13.1)	1 (0.3)
Rash	59 (16.6)	3 (0.8)	48 (13.4)	2 (0.6)
Hypothyroidism	55 (15.5)	0 (0.0)	46 (12.8)	0 (0.0)
Diarrhoea	53 (14.9)	4 (1.1)	36 (10.0)	2 (0.6)
Arthralgia	53 (14.9)	3 (0.8)	29 (8.1)	1 (0.3)
Vitiligo	45 (12.7)	0 (0.0)	42 (11.7)	0 (0.0)
Source: Long et al. 2022[18]				

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Nivolumab-relatlimab is a novel dual combination therapy of two immune checkpoint inhibitors. It is anticipated to provide similar efficacy to other currently used dual checkpoint inhibitors (i.e. nivolumab + ipilimumab), whilst demonstrating an improved safety profile. The availability of this treatment option would further enable clinicians to provide a more tailored approach to treatment, depending on factors such as the age of the patient, their performance status, existing comorbidities, and their ability to tolerate potential treatment toxicity.

Over a median follow-up of 19.3 months, results of the RELATIVITY-047 trial demonstrate that nivolumab-relatlimab has:

- Superior progression-free survival rates compared with nivolumab monotherapy
  - The median progression-free survival was 10.2 months in the nivolumab-relatlimab arm compared with 4.6 months in the nivolumab monotherapy arm[18]
- Improved overall survival compared with nivolumab monotherapy
  - A total of 137 (38.6%) patients died in the nivolumab-relatlimab arm compared with 160 (44.6%) patients in the nivolumab arm[18]
- Superior efficacy compared with nivolumab monotherapy across key patient subgroups. This was not dependent on a patient's PD-L1 status, LAG-3 status, American Joint Committee on Cancer (AJCC) metastatic stage, or *BRAF* mutational status[18]
- A similar effect on quality of life to nivolumab monotherapy, meaning nivolumab-relatlimab does not cause further detriment to the patient's quality of life[22]

When comparing nivolumab-relatlimab with nivolumab + ipilimumab, another dual checkpoint inhibitor therapy currently available for the treatment of advanced melanoma, a

comparison of trial results demonstrates that nivolumab-relatlimab has a similar efficacy to nivolumab + ipilimumab with a better safety profile.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Although treatment with dual checkpoint inhibitors has greatly improved outcomes in patients with advanced melanoma, this improved efficacy comes with high levels of toxicity, especially when compared with immuno-oncology monotherapies. Safety results for nivolumab-relatlimab versus nivolumab monotherapy, pembrolizumab monotherapy and nivolumab-ipilimumab are presented in Question 3g.

In some cases, high levels of toxicity can lead to the discontinuation of treatment. Compared with nivolumab monotherapy, nivolumab-relatlimab was associated with a higher percentage of patients discontinuing treatment due to side effects (15.2% versus 7.2%).[18]

While some long-term side effects are minimally bothersome to patients and easily managed, others may require prolonged courses of corticosteroids and other medications (which can have their own side effect profiles) and/or generally have significant impacts on quality of life.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness model approach

To assess the value and economic considerations of using nivolumab-relatlimab compared with nivolumab, nivolumab + ipilimumab or pembrolizumab, a cost-effectiveness model was developed. This model uses a simplified representation of advanced melanoma; it simulates a patient's progression through a set of distinct health

states. These health states are relevant to patients with advanced melanoma, and each health state is associated with a certain amount of costs and a certain quality of life.

The following health states were used in this cost-effectiveness model:

- **Progression-free:** a patient's disease is stable or responding to treatment and not actively progressing. Costs in this health state are associated with treatment received, treatment administration costs, management of disease and adverse events, with costs varying over time. Quality of life is higher compared with patients with progressed disease and is also affected by adverse events
- **Progressed disease:** a patient's disease is assumed to have progressed. Costs in this health state are associated with treatment received, treatment administration costs and management of disease. Quality of life is lower compared with patients with progression-free disease and is also affected by adverse events
- **Death:** an absorbing state. This state includes costs associated with palliative care and end-of-life costs

The model uses the clinical data available for nivolumab-relatlimab and the relevant comparators to estimate how fast a patient progresses through these different health states. More specifically, it uses the data on progression-free survival from clinical trials to estimate how long patients spend in the progression-free state, and the overall survival data to estimate how fast patients progress to death. The time spent in each health state is then adjusted for the quality of life of a patient in that health state, to estimate the total number of quality-adjusted life years (QALYs) gained by a patient as a result of the advanced melanoma treatment received. This is then compared with the total costs associated with that treatment (consisting of treatment costs, subsequent treatment costs, adverse event costs, and general costs associated with management of advanced melanoma such as routine visits and testing). This then allows for an assessment of whether the costs associated with using nivolumab-relatlimab are justifiable based on the additional QALYs patients gain.

Clinical benefits included in the model

The model predicted that treatment with nivolumab-relatlimab would lead to more clinical benefit (i.e. more QALYs) gained than treatment with all other comparators (please note that the exact QALY results are confidential). This benefit was mainly driven by the progression-free survival and overall survival benefit that nivolumab-relatlimab has over nivolumab and pembrolizumab, and the overall survival benefit over nivolumab + ipilimumab. This resulted in a longer time spent in the progression-free health state (compared with nivolumab and pembrolizumab), which was associated with a better overall quality of life, and a longer survival overall (compared to all comparators).

Costs included in the model

Nivolumab-relatlimab, nivolumab, ipilimumab, and pembrolizumab are subject to confidential price agreements with the NHS, so full cost information cannot be presented. However, broadly, treatment with nivolumab-relatlimab was associated with higher costs than treatment with nivolumab or pembrolizumab. This was mostly driven by higher treatment costs of nivolumab-relatlimab, and as patients live for longer, more disease management costs are accrued. Compared with nivolumab + ipilimumab, nivolumab-relatlimab was cost saving, due to the lower treatment costs of nivolumab-relatlimab compared with nivolumab + ipilimumab.

Model results

Overall, the model determined that treatment with nivolumab-relatlimab is associated with additional benefit to patients (more QALYs) compared with other comparators. Treatment with nivolumab-relatlimab is also associated additional costs, reflective of its status as a novel and innovative medicine. This result was shown across a range of sensitivity analyses which tested the model's assumptions and confirmed the robustness of the results.

Uncertainty

Although nivolumab-relatlimab was consistently was associated with additional benefit to patients (QALYs) and additional costs compared with all of the relevant comparators across a range of scenarios, some uncertainties remain. The key uncertainties are:

- **The clinical benefit compared with treatments not included in RELATIVITY-047.** There is no study that directly compares nivolumab-relatlimab with nivolumab + ipilimumab or pembrolizumab. The relative efficacy of these comparators was informed by a statistical analysis, which compared results across different trials
- **The generalisability to the UK.** As no UK-specific clinical data are available for any comparators, all efficacy data in the model are informed largely by global trials. UK clinical experts agreed that the studies used in the analysis are broadly aligned with UK practice. However, some of the patients in these trials received treatments that are not currently used in the UK
- **Long-term survival outcomes for nivolumab-relatlimab.** There are no data on the long-term outcomes of patients treated with nivolumab-relatlimab. Therefore, these long-term outcomes had to be extrapolated from data available from RELATIVITY-047. However, nivolumab-relatlimab contains nivolumab, which does have long-term evidence available – and UK clinicians anticipated nivolumab-relatlimab to provide long term survivorship (as seen with nivolumab). Alternative long-term extrapolations were explored in sensitivity analyses
- **Magnitude of deterioration in quality-of-life following disease progression.** Data on the quality of life of patients in the model are taken from responses of patients in the RELATIVITY-047 trial. However, it is known that as patients' conditions worsen, they are less likely to provide complete quality-of-life data as they are less able to complete questionnaires. This is reflected in the small difference between the progression-free and progressed disease quality of life included in the model. UK clinicians felt that this difference was too small and did not reflect clinical practice; therefore, the model has been tested using an alternative source of quality-of-life data, to see if this made any difference to the results. In testing this scenario, there was no major difference in quality-of-life outcomes

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Despite the impressive clinical success of immune checkpoint inhibitors, research has shown that some cancers, including melanoma, may become resistant to inhibitors that target the anti-PD-1 receptor. To enable more patients to benefit from immunotherapy,

alternative novel immune checkpoints inhibitors (such as LAG-3 inhibitors) have been investigated. The RELATIVITY-047 trial is the first trial to demonstrate that a fixed-dose combination of nivolumab, a PD-L1 inhibitor, and relatlimab, a LAG-3 inhibitor, can effectively treat advanced melanoma, thereby establishing LAG-3 as the third immune checkpoint inhibitor target in the melanoma pathway.

Furthermore, the choice of immuno-oncology treatment depends on many different factors and is chosen on a patient-by-patient basis. There is currently a need for additional novel treatments that are able to provide comparable efficacy outcomes to dual immuno-oncology therapy options currently available, with a more tolerable safety profile. Having access to another potential combination immuno-oncology therapy would provide a higher percentage of patients with advanced melanoma the opportunity to benefit from a more suitable treatment.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues were identified based on disability, gender reassignment, relationship status, pregnancy and maternity, race, religion or belief, sex and/or sexual orientation.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://toolbox.eupati.eu/resources/guidance-for-patient-involvement-in-hta/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/

- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: https://apps.who.int/iris/bitstream/handle/10665/332207/WHO-EURO-2005-611-40346-54035-eng.pdf?sequence=1&isAllowed=y

Patient groups and charities:

- Melanoma focus: https://melanomafocus.org/
- Melanoma fund: https://www.melanoma-fund.co.uk/
- Melanoma UK: https://www.melanomauk.org.uk/

Further information about untreated unresectable or metastatic melanoma:

- BMS melanoma clinical trials: https://www.bmsstudyconnect.com/us/en/health-studies/melanoma-clinical-trials.html
- Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/melanoma/stages-types

4b) Glossary of terms

Advanced cancer: Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumour, slow the growth of cancer cells, or relieve symptoms.[25]

Adverse event/side effect: An unexpected medical event that arises during treatment with a drug or other therapy. Adverse events can be classified as mild, moderate or severe.[25]

AJCC staging system: A system to describe the amount and spread of cancer in a patient's body, using TNM. T describes the size of the tumour and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body). This system was created and is updated by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). The AJCC staging system is used to describe most types of cancer. Also called TNM staging system.[25]

Asymptomatic: Having no signs or symptoms of disease.[25]

Clinical staging: A method used to find out the stage of cancer (amount or spread of cancer in the body) using tests that are done before surgery. These include physical exams, imaging tests, laboratory tests (such as blood tests), and biopsies.[25]

Clinical trial: A type of research that studies new tests and treatments and evaluates their effects on human health outcomes.[25]

Comorbidity: The condition of having two or more diseases at the same time.[25]

Complete response: The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission.[25]

Diagnosis: The process of identifying a disease, condition, or injury from its signs and symptoms. A health history, physical exam, and tests, such as blood tests, imaging tests, and biopsies, may be used to help make a diagnosis. [25]

Early-stage cancer: A term used to describe cancer that is early in its growth and may not have spread to other parts of the body. What is called early stage may differ between cancer types.[25]

Eligibility criteria: In clinical trials, requirements that must be met for a person to be included in a trial. These requirements help make sure that participants in a trial are like each other in terms of specific factors such as age, type and stage of cancer, general health, and previous treatment. When all participants meet the same eligibility criteria, it is more likely that results of the study are caused by the intervention being tested and not by other factors or by chance.[25]

Endpoint: In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumour.[25]

Financial burden: In medicine, a term used to describe problems a patient has related to the cost of medical care. Not having health insurance or having a lot of costs for medical care not covered by health insurance can cause financial problems and may lead to debt and bankruptcy. Financial burden can also affect a patient's quality of life and access to medical care. For example, a patient may not take a prescription medicine or may avoid going to the doctor to save money. Cancer patients are more likely to have financial burden than people without cancer. Also called economic burden, economic hardship, financial distress, financial hardship, financial stress, and financial toxicity.[25]

First-line therapy: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment. If it doesn't cure the disease or it causes severe side effects, other treatment may be added or used instead. Also called induction therapy, primary therapy, and primary treatment.[25]

Five-year survival rate: The percentage of people in a study or treatment group who are alive five years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.[25]

Health technology assessment (HTA): the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology.[26]

HTA bodies: Private or public organisations that perform HTAs.[26]

Immune checkpoint inhibitors: A type of drug that blocks proteins called checkpoints that are made by some types of immune system cells, such as T cells, and some cancer cells. These checkpoints help keep immune responses from being too strong and sometimes can keep T cells from killing cancer cells. When these checkpoints are blocked, T cells can kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include PD-1/PD-L1 and CTLA-4/B7-1/B7-2. Some immune checkpoint inhibitors are used to treat cancer.[25]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion.[25]

Intravenous (IV): Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein.[25]

Melanocyte: A cell in the skin and eyes that produces and contains the pigment called melanin.[25]

Melanoma: A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines.[25]

Meta-analysis: A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself.[25]

Metastatic: Having to do with metastasis, which is the spread of cancer from the primary site (place where it started) to other places in the body.[25]

Monotherapy: Therapy that uses one type of treatment, such as radiation therapy or surgery alone, to treat a certain disease or condition. In drug therapy, monotherapy refers to the use of a single drug to treat a disease or condition.[25]

Nivolumab and relatlimab: A combination of two drugs used to treat adults and children aged 12 years or older with melanoma that has spread or cannot be removed by surgery. It is also being studied in the treatment of other types of cancer. Nivolumab and relatlimab binds to the proteins PD-1 and LAG-3, which are found on T cells (a type of immune cell). Blocking these proteins may help the immune system kill cancer cells. The combination of nivolumab and relatlimab may work better than either drug alone. Nivolumab and relatlimab is a type of monoclonal antibody and a type of immune checkpoint inhibitor. Also called Opdualag.[25]

Performance status: A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.[25]

Quality of life: An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[27]

Randomised clinical trial: A study in which the participants are divided by chance into separate groups that compare different treatments or other interventions. Using chance to divide people into groups means that the groups will be similar and that the effects of the treatments they receive can be compared more fairly. At the time of the trial, it is not known which treatment is best. [25]

Unresectable: Unable to be removed by surgery.[25]

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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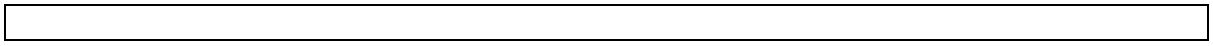


NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Clarification questions

May 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on clinical effectiveness data

RELATIVITY-047 trial design

A1. Please provide justification or references for the cure proportion assumptions behind the power calculations used to calculate the trial sample size (company submission [CS], Table 13).

The cure proportion assumptions used in the power calculations to calculate the trial sample size were informed by long-term data from the nivolumab and nivolumab + ipilimumab arms of Checkmate-067. The 5-year follow-up of CheckMate-067 presents PFS rates of 37% and 29% in the nivolumab + ipilimumab and nivolumab arms respectively (CS Document B, Figure 19).[1] Following the 5-year PFS there are relatively flat tails in the KM curves in both arms of CheckMate-067 thus the assumed cure rates of 40% and 30% in the nivolumab-relatlimab and nivolumab arms respectively was justified. This assumption is further supported by clinical expert opinion, NMA and adjusted ITC that suggested PFS and OS are both similar between nivolumab-relatlimab and nivolumab + ipilimumab (CS Document B, Sections B.2.9. and B.3.3).

RELATIVITY-047 trial patient flow

A2. Please provide the numbers of patients in the nivolumab-relatlimab and nivolumab arms who were treated with the study drug beyond initial disease progression.

In RELATIVITY-047 (October 2022 DBL), [redacted] of 359 patients ([redacted]%) in the nivolumab arm and [redacted] of 355 patients ([redacted]%) in the nivolumab-relatlimab arm received treatment beyond progression, though duration of this treatment was limited in both arms. Hence a greater number of patients remained on treatment beyond progression with nivolumab than with nivolumab-relatlimab.

[redacted]

Figure 1 and Figure 2 present a comparison of PFS and TTD over the duration of trial follow up in the nivolumab and nivolumab-relatlimab treatment arms respectively. Both figures illustrate that most patients in each arm stopped treatment well in advance of experiencing a progression event (this is more evident in the nivolumab-relatlimab arm relative to the nivolumab arm). The figures also demonstrate that in the cases where patients continued treatment beyond disease progression, patients only remained on treatment for a short duration after this point.

It should be noted that in the model base case a limit is built into TTD that does not allow it to exceed PFS and treatment stopping rules are also applied. This is to ensure that no patients remain on 1L treatment post-progression, in line with UK clinical practice (as detailed in CS Document B Section B.3.3.5). Based on the KM curves presented in

[redacted]

Figure 1 and Figure 2, inclusion of this limit should be considered

[redacted]

Figure 1: Nivolumab PFS & TTD comparison

Figure 2: Nivolumab-relatlimab PFS & TTD comparison

RELATIVITY-047 trial efficacy results

A3. Priority question: The trial did not include any patients aged 12 years to 18 years. Please provide clinical effectiveness evidence of nivolumab-relatlimab

for patients aged 12 years to 18 years with untreated unresectable or metastatic melanoma.

There was no clinical efficacy/safety data for nivolumab-relatlimab generated in adolescents with untreated unresectable or metastatic melanoma. Below is an excerpt from the Opdualag EU published EPAR (https://www.ema.europa.eu/en/documents/assessment-report/opdualag-epar-public-assessment-report_en.pdf) which provides rationale for extrapolating the benefit in adults to adolescents.

"*3.7.3. Additional considerations on the benefit-risk balance*

No adolescents were included in the clinical studies. Given the similarity of disease histology, genetic background, treatment and prognosis of metastatic melanoma for adults and adolescents, and sufficiently comparable predicted drug exposure in adults and adolescents, based on popPK simulations in patients weighing at least 30 kg, extrapolation of efficacy and safety from adults to the adolescent population is considered acceptable. In these simulations, both the situation of a reduced clearance and volume of distribution of relatlimab and nivolumab, as well as the situation of a comparable clearance and volume of distribution in adolescents and adults, was simulated. In both cases the exposure is considered sufficiently comparable between adolescent and adult patients. Therefore, inclusion of adolescents 12 years of age and older in the indication is considered approvable. The available safety data of nivolumab in adolescents, indicate a comparable short term safety profile for adolescents as for adults. Given that nivolumab and relatlimab are both check-point inhibitors, also for relatlimab a comparable short term safety profile for adolescents and adults may be expected in case of comparable exposure. Long-term safety data are missing, especially the long-term effect of endocrine AEs might be different between adults and adolescents. Given the poor prognosis of adolescents with metastatic or unresectable (advanced melanoma), the uncertainty regarding the long-term toxicity profile is not considered a major concern. In addition, long-term safety will be followed - Assessment report EMA/720884/2022 Page 146/147 up post approval (cat 3 study)."

A4. Priority question: Please provide Kaplan-Meier (K-M) estimates for the nivolumab-relatlimab and nivolumab arms (data cut-off date 27 October 2022) for the following endpoints:

- **progression-free survival (blinded independent central review [BICR]; primary definition)**
- **progression-free survival (investigator; primary definition)**
- **overall survival (OS)**
- **time to treatment discontinuation (TTD)**

For each time-to-event endpoint, please include:

a) **a table showing, for each event or censored individual:**
   - **survival estimate at time t**
   - **standard error (SE) of survival estimate at time t**
   - **number at risk at time t**
   - **cumulative number of events at time t**
   - **censoring at time t**

b) **hazard plots for each outcome (if not already presented in the CS)**

The embedded files below provide the requested data detailed in A4 (a) for PFS (per BICR; the primary endpoint of RELATIVITY-047), OS and TTD.

KM estimates PFS BICR.xlsx KM estimates OS.xlsx KM estimates TTD.xlsx

As requested in A4 (d), smoothed hazard plots for each outcome (PFS [per BICR], OS and TTD) are presented in Figure 3, Figure 6, and Figure 7, respectively. In the Figures with long-term follow-up, hazards for the UK general population are also included for reference.

PFS (per BICR) hazards from the trial data converge towards the UK general population, appearing to reach the general population hazards at the end of the

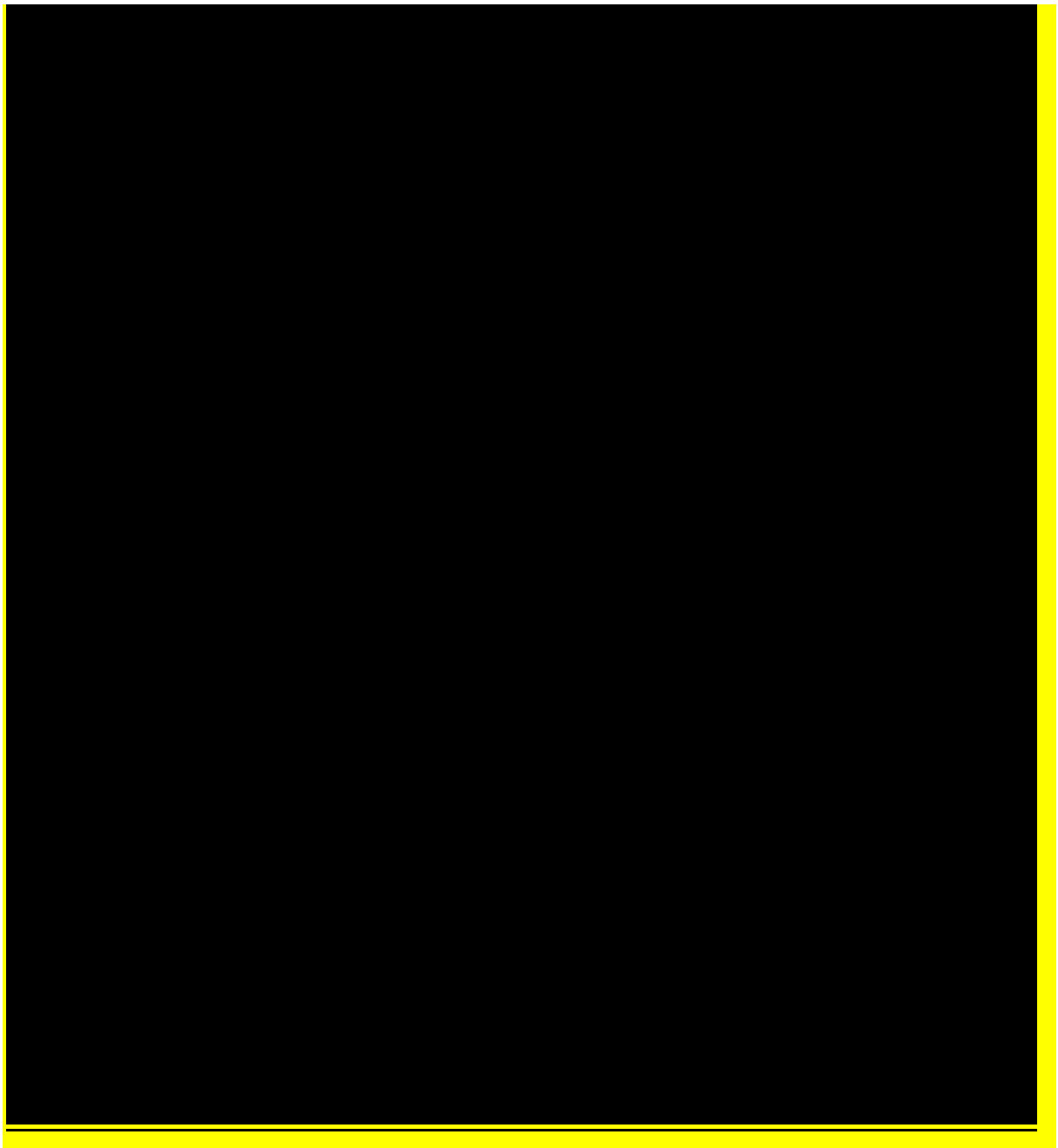
follow-up period (Figure 3). In reviewing Figure 3, it should be noted that smoothed hazards are less reliable at the tails given the smaller numbers of patients at risk and smaller number of events. Hence it is important not to over-interpret any differences at the end of follow-up given the uncertainty in these estimates.

Figure 4 presents PFS (per BICR) smoothed hazards up to 21 months (corresponding to the minimum follow-up in RELATIVITY-047) in which there are greater number of patients at risk. This demonstrates an early separation in favour of nivolumab-relatlimab at the start of follow-up, followed by gradual convergence of the two curves. The KM curves presented in Figure 5 show the number of patients at risk and the cumulative number of events at each timepoint, in each treatment arm. As can be observed, at 18 months, patients in the nivolumab-relatlimab arm have experienced 188/219 = 85.8% of the total observed events, compared to 226/244 = 92.6% for nivolumab. So, after 18 months, there is a higher proportion of the events in the nivolumab-relatlimab arm compared to nivolumab, i.e. 14.2% for nivolumab-relatlimab vs 7.4% for nivolumab. This likely increases the hazards for nivolumab-relatlimab relative to nivolumab after this point. However, this is because the events occur earlier in the nivolumab arm, whereas the events occur more slowly in the nivolumab-relatlimab arm. Figure 5 also demonstrates that after the initial early separation, PFS remains higher for nivolumab-relatlimab than nivolumab at all subsequent time-points.

Figure 3: PFS (per BICR) smoothed hazards for nivolumab-relatlimab and nivolumab compared to general population hazards for the UK

Figure 4: PFS (per BICR) smoothed hazards for nivolumab-relatlimab and nivolumab (up to minimum follow up [21 months])

Figure 5: PFS (per BICR) Kaplan-Meier curves



The OS nivolumab smoothed hazards are higher than nivolumab-relatlimab across the entire follow-up period (Figure 6). Nivolumab-relatlimab hazards approach the general population hazards at the end of the follow-up period.

Figure 6: OS smoothed hazards for nivolumab-relatlimab and nivolumab compared to general population hazards for the UK

The TTD hazards for both treatments decrease during the follow-up period (Figure 7).

Figure 7: TTD smoothed hazards for nivolumab-relatlimab and nivolumab

A5. Priority question: If it is not possible to provide K-M data as per question A4, please provide the following summary results for PFS per investigator assessment for the nivolumab-relatlimab and nivolumab trial arms (primary definition, data cut-off date 27 October 2022):

a) **median and 95% confidence interval (CI) for each arm**

b) **number of events for each arm**

c) **hazard ratio (HR) and 95% CI**

d) **K-M plots of:**

- **PFS investigator (nivolumab-relatlimab versus nivolumab)**
- **PFS investigator, OS and TTD for nivolumab-relatlimab**
- **PFS investigator, OS and TTD for nivolumab**

e) **hazard plots for each arm**

f) **plots of Schoenfeld residuals versus time, log cumulative hazards versus log time and results of the Grambsch-Therneau test**

The assessment of nivolumab-relatlimab should utilise PFS per BICR to inform PFS estimates as this is the primary study endpoint in RELATIVITY-047 for which the trial was appropriately powered and assessment was conducted by a blinded third party. PFS per investigator assessment (IA) was an exploratory endpoint for which the RELATIVITY-047 trial was not powered to demonstrate differences by treatment. PFS per BICR is also most commonly viewed as the gold standard for disease progression assessment as it is more objective than PFS per IA.[2] It is well established that PFS per BICR provides a more robust and less biased assessment of progression (i.e. progression events) than PFS per IA. This view of utilising BICR in cancer drug trials is well advocated by EMA and FDA guidance.[3, 4] BICR is favoured as it removes assessment bias between readers, reduces variability and increases accuracy in determining if a patient has progressed, thus counteracting many issues that can often arise from IA.

Concordance PFS assessment per BICR versus PFS per IA available from the October 2021 DBL demonstrates that concordance is generally high in both

treatment arms (Table 1 and Table 2). From a relative perspective, concordance was higher in the nivolumab arm ([redacted]%) than the nivolumab-relatlimab arm ([redacted]%). In the nivolumab arm, PFS per IA identified [redacted] events (compared to BICR [redacted]) and in the nivolumab-relatlimab arm using PFS per IA identified [redacted] events than PFS per BICR ([redacted]). Therefore, PFS per IA data should be considered biased [redacted]. Taken together with the fact that PFS per BICR was the powered primary endpoint while PFS per IA was an exploratory endpoint, the reduced bias for PFS per BICR vs PFS per IA, and [redacted], we reinforce that PFS per BICR is appropriate for calculating PFS within this assessment.

Table 1: Concordance between PFS by BICR and PFS assessment by investigator, primary definition all randomised subjects; nivolumab (n = 359)

	PFS Assessment by BICR		
	Progression	**Death**	**Censored**
PFS by investigator (%)			
Progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]
Agreement between BICR and Investigator-assessed for event (PD or death) and censoring (%)	[redacted]		
# Event (PD or death) per BICR / # Event (PD or death) per investigator assessment	[redacted]		
Key: BICR, blinded independent central review; PD, progressed disease; PFS, progression-free survival			

Table 2: Concordance between PFS by BICR and PFS assessment by investigator, primary definition all randomised subjects; nivolumab-relatlimab (n = 355)

	PFS Assessment by BICR		
	Progression	**Progression**	**Progression**
PFS by investigator (%)			
Progression	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]
Agreement between BICR and Investigator-assessed for event (PD or death) and censoring (%)	[redacted]		
# Event (PD or death) per BICR / # Event (PD or death) per investigator assessment	[redacted]		

Key: BICR, blinded independent central review; PD, progressed disease; PFS, progression-free survival

Whilst PFS per IA was used in the ITC (Section B.2.9.2 of the submission), this was due to a lack of PFS per BICR for a similar amount of follow-up between CheckMate 067 and the October 2022 DBL of RELATIVITY-047 which forms the basis of this submission. In particular, PFS per BICR was only available from CheckMate-067 for the first data cut, which had a limited duration of follow-up (see Figure 30). We recognize and reiterate that PFS per IA was an exploratory endpoint for which the RELATIVITY-047 trial was not powered, though this ITC was provided to adequately compare a similar amount of follow-up between the two trials. An adjusted ITC, using PFS per BICR from both trials, as based on an earlier database lock of RELATIVITY-047 (October 2021) and the February 2015 DBL from CheckMate 067, yielded the same conclusions as the adjusted ITC based on PFS per IA (these data are provided in detail in response to Priority question A.17). It is important to note that the February 2015 database lock from CheckMate-067 was the only lock where PFS per BICR data were available, and therefore it was not possible to update these analyses using later database locks from either of the two trials.

The assessment of nivolumab-relatlimab should use the primary study endpoint for which the RELATIVITY-047 trial was appropriately powered (i.e. PFS per BICR [gold

standard]). Summary results for PFS by IA that are currently available are provided below. Table 3 presents the results for PFS by IA for the ITT population of the RELATIVITY-047 trial. The median PFS was [redacted] months (95% CI [redacted], [redacted]) with nivolumab-relatlimab, compared with [redacted] months (95% CI [redacted], [redacted]) with nivolumab (HR [redacted]; 95% CI [redacted], [redacted]).

Table 3: Analysis of PFS by IA in the RELATIVITY-047 trial (ITT population)

	Nivolumab-relatlimab (n = [redacted])	Nivolumab (n = [redacted])
Number of events	[redacted]	[redacted]
Median PFS (95% CI), months	[redacted]	[redacted]
PFS HR (95% CI)	[redacted]	

Key: CI, confidence interval; IA, investigator assessment; ITT, intention to treat; PFS, progression-free survival.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)

Finally, it is noted that within the cost-effectiveness analysis, alternative models for the analysis of PFS had minimal impact on estimates of cost-effectiveness (Section B.3.10.2) as the model is largely driven by the OS extrapolations. Hence it is anticipated that cost-effectiveness results would be robust to different definitions of PFS.

To conclude, PFS per BICR is the most appropriate choice as it was the statistically powered primary endpoint for this trial. As noted above, the model is largely driven by the OS extrapolations, therefore cost-effectiveness results are expected to be robust to different definitions of PFS. PFS per IA is an exploratory endpoint that [redacted] and is utilised where BICR results are not readily available. For these reasons outlined above, results per IA have not been provided.

RELATIVITY-047 trial safety and tolerability results

A6. In the nivolumab-relatlimab draft summary of product characteristics (SmPC, Table 1), for a number of adverse events (AEs), it is recommended that (a) treatment with nivolumab-relatlimab should be stopped until AEs resolve and (b) treatment with

nivolumab-relatlimab should be permanently discontinued. In a similar format to tables in the CS (see Table 19: Summary of AEs [intention-to-treat [ITT] population] and Table 20: Frequently reported TRAEs [ITT population]), please provide:

- the number and proportion of patients who stopped treatment until AEs had resolved and then resumed treatment
- the most common treatment-related adverse events (TRAEs) that resulted in patients stopping treatment until AEs had resolved and then resumed treatment
- the most common TRAEs that resulted in patients permanently discontinuing treatment

AEs in which it is recommended that treatment is stopped until the AE is resolved is also referred to as a dose delay. A dose was considered delayed if the delay in treatment with nivolumab-relatlimab or nivolumab exceeded 3 days. In total, 168 (47.3%) patients in the nivolumab-relatlimab arm and 163 (45.4%) patients in the nivolumab arm experienced at least one dose delay.[5]

We acknowledge the EAG's request for the company to provide data on the most common TRAEs that resulted in patients stopping treatment until AEs had resolved and then resumed treatment. This data was not attainable in the short timeframe to respond to EAG clarification questions, however the company aim to provide this data prior to technical engagement.

Table 4 presents the reported TRAEs that resulted in permanent discontinuation of study treatment.

Table 4: Frequently reported TRAEs that resulted in permanent discontinuation of treatment

	Nivolumab-relatlimab (n = 355)		Nivolumab (n = 359)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
TRAEs that resulted in patients permanently discontinuing treatment				
Myocarditis				
Pneumonitis				
Colitis				
Diarrhoea				

	Nivolumab-relatlimab (n = 355)		Nivolumab (n = 359)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
ALT increased				
Adrenal insufficiency				
Fatigue				
Renal failure				
Encephalitis				
Arthralgia				
Myositis				
Troponin increased				
Troponin T increased				

Key: AE, adverse event; TRAE, treatment-related adverse event;
Source: RELATIVITY-047 CSR addendum 02 supplementary tables.[5]

RELATIVITY-047 trial patient reported outcomes

A7. Please provide FACT-M physical well-being and FACT-M functional well-being on-treatment results for the nivolumab-relatlimab and nivolumab arms.

Table 5 and Table 6 present the FACT-M physical well-being on-treatment results and Table 7 and Table 8 present the FACT-M functional well-being on-treatment results for the nivolumab-relatlimab and nivolumab arms of RELATIVITY-047. Please note, the data presented in these tables is for the October 2021 database lock; these analyses have not been performed for the most recent October 2022 database lock. Graphical representations of these data are presented in Appendix N.2.2 of the CS.

Table 5: FACT-M physical well-being observed score and change from baseline by visit

	Nivolumab-relatlimab			Nivolumab		
	No. of patients evaluated at visit	Mean observed value	Mean change from baseline	No. of patients evaluated at visit	Mean observed value	Mean change from baseline
Baseline						
Week 8						
Week 16						
Week 24						
Week 32						
Week 40						
Week 48						

Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 144	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: FACT-M, Functional Assessment of Cancer Therapy-Melanoma.
Source: RELATIVITY-047 CSR HRQoL data (October 2021 DBL)[6]

Table 6: FACT-M physical well-being LS mean change from baseline

	LS mean		Difference
	Nivolumab-relatlimab	Nivolumab	
Week 8	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]
Week 128	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]
Week 144	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]

Key: FACT-M, Functional Assessment of Cancer Therapy-Melanoma; LS, least squares.
Source: RELATIVITY-047 CSR HRQoL data (October 2021 DBL)[6]

Table 7: FACT-M functional well-being observed score and change from baseline by visit

	Nivolumab-relatlimab	Nivolumab

	No. of patients evaluated at visit	Mean observed value	Mean change from baseline	No. of patients evaluated per visit	Mean observed value	Mean change from baseline
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 144	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: FACT-M, Functional Assessment of Cancer Therapy-Melanoma.
Source: RELATIVITY-047 CSR HRQoL data (October 2021 DBL)[6]

Table 8: FACT-M functional well-being LS mean change from baseline

	LS mean		Difference
	Nivolumab-relatlimab	Nivolumab	
Week 8	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]
Week 56	[redacted]	[redacted]	[redacted]
Week 64	[redacted]	[redacted]	[redacted]
Week 72	[redacted]	[redacted]	[redacted]
Week 80	[redacted]	[redacted]	[redacted]
Week 88	[redacted]	[redacted]	[redacted]
Week 96	[redacted]	[redacted]	[redacted]
Week 104	[redacted]	[redacted]	[redacted]
Week 112	[redacted]	[redacted]	[redacted]
Week 120	[redacted]	[redacted]	[redacted]

Week 128	[redacted]	[redacted]	[redacted]
Week 136	[redacted]	[redacted]	[redacted]
Week 144	[redacted]	[redacted]	[redacted]
Week 152	[redacted]	[redacted]	[redacted]
Key: FACT-M, Functional Assessment of Cancer Therapy-Melanoma; LS, least squares. **Source:** RELATIVITY-047 CSR HRQoL data (October 2021 DBL)[6]			

A8. It is stated in the RELATIVITY-047 trial protocol that health-related quality of life (HRQoL) data were collected from patients who had stopped treatment at follow-up (FACT-M and EQ-5D-3L data) and survival follow-up (FACT-M melanoma subscale and EQ-5D-3L data) visits. Please provide HRQoL results for off-treatment patients including the numbers and proportion of patients in the nivolumab-relatlimab and nivolumab arms who completed the questionnaires at each timepoint.

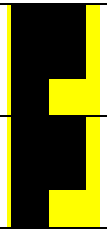
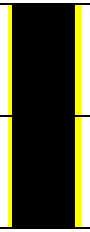
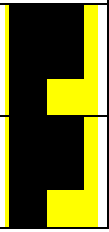
The completion rates for the EQ-5D-3L questionnaire for the ITT population are shown in Table 9 for each visit. The completion rate is defined as the number of complete and valid questionnaires out of the number of patients in the study for that visit. The responses for the completed questionnaires listed here are the responses used in the later analyses. For the follow-up visits, the completion rates were approximately [redacted]%.

Table 9: Completion rates for the EQ-5D-3L questionnaire

	Completion rate	
Visit	**Relatlimab + Nivolumab**	**Nivolumab**
FOLLOW-UP 1	[redacted]	[redacted]
FOLLOW-UP 2	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 1	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 2	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 3	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 4	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 5	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 6	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 7	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 8	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 9	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 10	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 11	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 12	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 13	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 14	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 15	[redacted]	[redacted]

Summary statistics for the EQ-5D-3L responses for the ITT population using the Dolan [7] value set for the United Kingdom are shown in Table 10. The summary statistics are provided across all visits, by treatment arm and by treatment status (on treatment / off treatment). Patients on treatment overall had a higher utility of [redacted] compared to [redacted] for patients off treatment.

Table 10: Summary statistics for EQ-5D-3L utilities using the United Kingdom value set

	Relatlimab + Nivolumab				Nivolumab				Overall			
	N	Mean (SD)	Median (IQR)	Min - Max	N	Mean (SD)	Median (IQR)	Min - Max	N	Mean (SD)	Median (IQR)	Min - Max
Treatment status												
On treatment												
Off treatment												

N = total number of assessments across all patients and visits; SD = Standard deviation; IQR = Interquartile range; Min = Minimum; Max = Maximum; PF = Progression-free; PD = Progressed disease

Network meta-analyses (NMAs)

A9. Priority question: Please conduct NMAs to estimate time-varying and constant HRs using PFS per investigator assessment data from all four trials included in the NMAs (RELATIVITY-047 data cut-off date 27 October 2022). KEYNOTE-006 trial PFS per investigator assessment results are reported in the Robert 2019[8] paper. Please provide HRs over time and cumulative survival over time for all fixed-effects fractional polynomial (FP) models for PFS per investigator assessment considered to provide a plausible fit.

As fully explained in response to A5, this assessment should utilize PFS per BICR from RELATIVITY-047 as this is the primary endpoint for which the study was powered and PFS per BICR provides a less biased assessment than PFS per IA. PFS per IA should not be considered in the assessment of nivolumab-relatlimab. In addition, while there is generally high concordance between BICR and IA on both treatment arms of RELATIVITY-047, use of PFS per IA data would be biased in [redacted].

We also wish to clarify that for the presented NMA evidence from the KEYNOTE-006 trial used PFS per IA results from Robert 2019[8], not PFS per BICR as incorrectly stated in the CS Appendix D.4.1.2. Table 11. It is worth noting that the HR for PFS per IA for pembrolizumab versus IPI from Robert 2019[8] (HR: 0.57 [95% CI: 0.60-0.88) is consistent with the HR for PFS per BICR for pembrolizumab versus IPI from Robert 2015[9] (HR=0.58 [95% CI: 0.46-0.72]); therefore, as the NMA uses Robert 2019 and the data are consistent, there is no need to provide a PFS per IA NMA for reasons explained above as PFS per BICR from RELATIVITY-047 is most appropriate for use in this submission.

A10. Priority question: Please provide PFS and OS results (HRs over time and cumulative survival over time [CS, Table 17, Figure 8 and Figure 9 format]) for the 2nd, 3rd and 4th best fitting fixed-effects FP models referred to in the CS (Appendix D, Section D.4.1.4).

The best fitting models were selected based on both DIC value (with lower DIC indicating better fit), visual fit and the clinical plausibility of modelled curves. The DIC

values for the 4 best fitting models for OS are shown in Table 11. As can be observed, the DIC values were similar across the 4 best fitting models for OS, therefore visual inspection and clinical plausibility were essential to select the base case model. For OS, the model with the 2nd lowest DIC was selected as the base case model due to the implausible survival curves in the model with the lowest DIC, specifically with respect to modelling pembrolizumab. Similar implausible estimates were also generated from the 3rd and 4th best fitting model and therefore these models were deprioritised. The selected OS NMA model was also validated against the observed KM data from the trial (see CS Appendix O.3 Figure 46 and Figure 47). For this reason, the 3rd and 4th best fitting models were not considered. The time-varying hazard ratios for each of the 4 best fitting models are presented over time in Table 12. Figure 8 to Figure 11 graphically present the HRs over time of nivolumab-relatlimab compared with nivolumab, nivolumab + ipilimumab and pembrolizumab and the survival curves of nivolumab-relatlimab, nivolumab, nivolumab + ipilimumab and pembrolizumab when fractional polynomial models are applied to the pooled nivolumab data from all nivolumab arms included in the network for the 1st, 3rd and 4th best fitting models of OS by DIC.

Table 11: Fractional polynomial models of OS by DIC

Model fit	Model	DIC
1st best fitting	P1=1, P2=-1, scale and 1st shape	875.21
2nd best fitting*	P1=1, P2=-1, scale and 2nd shape	875.87
3rd best fitting	P1=0, P2=0, scale and 2nd shape	877.32
4th best fitting	P1=0, P2=0, scale and 1st shape	877.43
Note: *Base case model		

Table 12: OS comparison of time-varying hazard ratios from the 4 best fitting models by DIC

	RELA + NIVO vs.	Time-varying HR (95% CrI)									
Model – presented in order of DIC		**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**	**30 months**	**36 months**	**42 months**	**48 months**
P1=1, P2=-1, scale and 1st shape	**NIVO3**	[redacted]									
P1=1, P2=-1, scale and 2nd shape*		[redacted]									
P1=0, P2=0, scale and 2nd shape		[redacted]									
P1=0, P2=0, scale and 1st shape		[redacted]									
P1=1, P2=-1, scale and 1st shape	**PEM**	[redacted]									
P1=1, P2=-1, scale and 2nd shape*		[redacted]									
P1=0, P2=0, scale and 2nd shape		[redacted]									
P1=0, P2=0, scale and 1st shape		[redacted]									

P1=1, P2=-1, scale and 1st shape	**NIVO1 + IPI3**	[redacted]									
P1=1, P2=-1, scale and 2nd shape*		[redacted]									
P1=0, P2=0, scale and 2nd shape		[redacted]									
P1=0, P2=0, scale and 1st shape		[redacted]									

Note: All bolded values are statistically significant at the 0.05 significance level; Abbreviations: CrI – credible interval; HR – hazard ratio

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.

***Base case model: P1=1, P2=-1, scale and 2nd shape**

Figure 8: Results of fixed effects fractional polynomial model for OS; HR over time (P1=1, P2=-1; scale and 1st shape) – 1st best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 9: Results of fixed effects fractional polynomial model for OS; survival curves relative to pooled NIVO3 (P1=1, P2=-1; scale and 1st shape) – 1st best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 10: Results of fixed effects fractional polynomial model for OS; HR over time (P1=0, P2=0; scale and 1st shape) – 3rd best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 11: Results of fixed effects fractional polynomial model for OS; survival curves relative to pooled NIVO3 (P1=0, P2=0; scale and 1st shape) – 3rd best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 12: Results of fixed effects fractional polynomial model for overall survival; HR over time (P1=0, P2=0; scale and 2nd shape) – 4th best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 13: Results of fixed effects fractional polynomial model for OS; survival curves relative to pooled NIVO3 (P1=0, P2=0; scale and 2nd shape) – 4th best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

For PFS the best fitting models were also selected based on both DIC value (with lower DIC indicating better fit), visual inspection and the clinical plausibility of modelled curves. The DIC values for the 4 best fitting models for PFS are shown in Table 13. As can be observed, the DIC values were similar across the 2 best fitting models, but DIC values for the 3rd and 4th best fitting models were almost 100 points higher, indicating poorer fit. For this reason, the 3rd and 4th best fitting models were deprioritised. A comparison of the time varying HRs from the 4 best fitting models shown in Table 14. For PFS, the model with the lowest DIC was selected as the base case model due to the implausible survival curves in the model with the 2nd lowest DIC (specifically, HRs favouring nivolumab over nivolumab-relatlimab were observed after 18 months, which was also observed in the 4th best fitting model). The selected PFS NMA model was also validated against the observed KM data from the trial (see CS Appendix O.3 Figure 48 and Figure 49). For this reason, the 2nd, 3rd and 4th best fitting models were not considered for the analysis. Figure 14 to Figure 19 graphically present the HRs over time of nivolumab-relatlimab compared with nivolumab, nivolumab + ipilimumab and pembrolizumab and the survival curves of nivolumab-relatlimab, nivolumab, nivolumab + ipilimumab and pembrolizumab when fractional polynomial models are applied to the pooled nivolumab data from all nivolumab arms included in the network for the 2nd, 3rd and 4th best fitting models of PFS by DIC.

Table 13: Fractional polynomial models of PFS by DIC

Model fit	Model	DIC
1st best fitting*	P1=0, P2=-1, scale and 2nd shape	1423.59
2nd best fitting	P1=0, P2=-1, scale and 1st shape	1425.59
3rd best fitting	P1=0, P2=-0.5, scale and 2nd shape	1528.64
4th best fitting	P1=0, P2=-0.5, scale and 1st shape	1529.51
Note: *Base case model		

Table 14: PFS comparison of time-varying hazard ratios from the 4 best fitting models by DIC

	RELA + NIVO vs.	Time-varying HR (95% CrI)									
Model – presented in order of DIC		3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
P1=0, P2=-1, scale and 2nd shape*	NIVO3										
P1=0, P2=-1, scale and 1st shape											
P1=0, P2=-0.5, scale and 2nd shape											
P1=0, P2=-0.5, scale and 1st shape											
P1=0, P2=-1, scale and 2nd shape*	PEM										
P1=0, P2=-1, scale and 1st shape											
P1=0, P2=-0.5, scale and 2nd shape											
P1=0, P2=-0.5, scale and 1st shape											

P1=0, P2=-1, scale and 2nd shape*	**NIVO1 + IPI3**										
P1=0, P2=-1, scale and 1st shape											
P1=0, P2=-0.5, scale and 2nd shape											
P1=0, P2=-0.5, scale and 1st shape											

Note: All bolded values are statistically significant at the 0.05 significance level; Abbreviations: CrI – credible interval; HR – hazard ratio.

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab

***Base case model: P1=0, P2=-1, scale and 2nd shape**

Figure 14: Results of fixed effects fractional polynomial model for PFS; HR over time (P1=0, P2=-1; scale and 1st shape) – 2nd best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 15: Results of fixed effects fractional polynomial model for PFS; survival curves relative to pooled NIVO3 (P1=0, P2=-1; scale and 1st shape) – 2nd best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 16: Results of fixed effects fractional polynomial model for PFS; HR over time (P1=0, P2=-0.5; scale and 2nd shape) – 3rd best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 17: Results of fixed effects fractional polynomial model for PFS; survival curves relative to pooled NIVO3 (P1=0, P2=-0.5; scale and 2nd shape) – 3rd best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 18: Results of fixed effects fractional polynomial model for PFS; HR over time (P1=0, P2=-0.5; scale and 1st shape) – 4th best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

Figure 19: Results of fixed effects fractional polynomial model for PFS; survival curves relative to pooled NIVO3 (P1=0, P2=-0.5; scale and 1st shape) – 4th best fitting model

Key: NIVO3, nivolumab monotherapy 3 mg/kg; NIVO1+IPI3, nivolumab 1 mg/kg + ipilimumab 3 mg/kg; PEM, pembrolizumab; RELA+NIVO, nivolumab-relatlimab.
Notes: The reference curve consists of the pooled nivolumab data from all nivolumab arms included in the evidence network.

A11. Priority question: Please provide plots of Schoenfeld residuals versus time and log cumulative hazards versus log time for PFS per investigator assessment and OS from the CheckMate067, CheckMate069 and KEYNOTE-006 trials.

Details on proportional-hazards tests (Grambsch and Therneau test, Wald test) for OS and PFS for the studies included in the NMA are provided in the submitted Appendix Section D.4.1.2. Schoenfeld residual plots for each of the 4 trials informing the analyses are presented below, by outcome:

Figure 20: PFS Schoenfeld residuals, CheckMate 067; ipilimumab vs nivolumab

Figure 21: PFS Schoenfeld residuals, CheckMate 067; nivolumab + ipilimumab vs. ipilimumab

Figure 22: PFS Schoenfeld residuals, CheckMate 067; nivolumab + ipilimumab vs. nivolumab

Figure 23: PFS Schoenfeld residuals, CheckMate 069; nivolumab + ipilimumab vs. ipilimumab

Figure 24: PFS Schoenfeld residuals, KEYNOTE 006; pembrolizumab vs. ipilimumab

Figure 25: OS Schoenfeld residuals, CheckMate 067; ipilimumab vs. nivolumab

Figure 26: OS Schoenfeld residuals, CheckMate 067; nivolumab + ipilimumab vs. ipilimumab

Figure 27: OS Schoenfeld residuals, CheckMate 067; nivolumab + ipilimumab vs nivolumab

Figure 28: OS Schoenfeld residuals, CheckMate 069; nivolumab + ipilimumab vs. ipilimumab

Figure 29: OS Schoenfeld residuals, KEYNOTE 006; pembrolizumab vs. ipilimumab

A12. Priority question: Please provide the summary data included in the OS and PFS NMAs assuming constant hazards (i.e., HR with 95% CIs) and the NMAs of safety outcomes (i.e., numbers of events and numbers of patients or odds ratios with 95% CIs). Please also provide summary data sources, or, when patient-level data were used to calculate the summary data, the date of database lock.

Table 15 presents the summary data for OS and PFS as well as the data sources informing both the time-varying and constant hazards NMA.

Table 16 presents the summary of safety data and sources included in the NMA of safety outcomes.

Table 15: Summary of survival NMA data sources

Trial	Analysis	Reference	OS, value	OS, data source	PFS, value	PFS, data source
RELATIVITY 047	constant	RELA + NIVO vs NIVO3	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)
	time-varying		IPD	BMS 2022 (OCT 22 DBL)	IPD	BMS 2022 (OCT 22 DBL)
CheckMate 067	constant	NIVO1 + IPI3 vs IPI3	0.53 (0.44, 0.65)	Hodi 2022	0.42 (0.35,0.51)	Hodi 2022
		NIVO3 vs IPI3	0.63 (0.52, 0.77)	Hodi 2022	0.53 (0.44, 0.64)	Hodi 2022
	time-varying	NIVO1 + IPI3 vs IPI3	KM curve	Hodi 2022	KM curve	Hodi 2022
		NIVO3 vs IPI3	KM curve	Hodi 2022	KM curve	Hodi 2022
CheckMate 069	constant	NIVO1 + IPI3 vs IPI3	0.74 (0.43,1.26)	Hodi 2016	0.36 (0.22, 0.56)	Hodi 2016
	time-varying		IPD	BMS 2021	KM curve	BMS 2021
KEYNOTE 006	constant	PEM vs IPI3	0.73 (0.57, 0.92)	Robert 2019	0.54 (0.44, 0.67)	Robert 2019
	time-varying		KM curve	Robert 2019	KM curve	Robert 2019

Key: DBL, database lock; IPD, individual patient data; KM, Kaplan-Meier; NIVO, nivolumab; NIVO3, nivolumab; NIVO1 +IPI3, nivolumab +ipilimumab; OS, overall survival; PFS, progression-free survival; RELA + NIVO, nivolumab-relatlimab.

Table 16: Summary of safety NMA data sources

Trial		Grade 3-4 AEs, value	Grade 3-4 AEs, data source	Grade 3-4 TRAEs, value	Grade 3-4 TRAEs, data source	Overall discon, value	Overall discon, data source	DAES, value	DAEs, data source	DTRAEs, value	DTRAEs, data source
RELATIVITY 047	RELA+NIVO	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)
	NIVO3	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)	[redacted]	BMS 2022 (internal deck)
CheckMate 067	IPI3	173 (55.6)	Larkin 2015	86 (28)	Wolchok 2021	311 (100)	IPD	58 (19)	IPD	47 (15)	IPD
	NIVO3	13.6 (43.5)	Larkin 2015	74 (24)	Wolchok 2021	301 (96.16)	IPD	157 (50)	IPD	44 (14)	IPD
	NIVO1+IPI3	215 (68.7)	Larkin 2015	186 (59)	Wolchok 2021	289 (92.33)	IPD	53 (17)	IPD	131 (42)	IPD
CheckMate 069	NIVO1+IPI3	--	--	51 (54)	Hodi 2016	81 (86.17)	Hodi 2016	52 (55)*	Hodi 2016	46 (49)	Hodi 2016
	IPI3	--	--	9 (20)	Hodi 2016	40 (86.95)	Hodi 2016	13 (28)*	Hodi 2016	10 (22)	Hodi 2016
KEYNOTE 006	PEM	--	--	50 (20)	Robert 2019	101 (36.33)	Robert 2019	35 (14)	Robert 2019	23 (9)	Robert 2019
	IPI3	--	--	96 (17)	Robert 2019	430 (77.47)	Robert 2019	81 (15)	Robert 2019	55 (10)	Robert 2019

Key: AE, adverse event; DAE, discontinuation due to an adverse event; DBL, database lock; DTRAE, discontinuation due to a treatment-related adverse event; IPD, individual patient data; KM, NIVO, nivolumab; NIVO3, nivolumab; NIVO1 +IPI3, nivolumab +ipilimumab; RELA + NIVO, nivolumab-relatlimab; TRAE, treatment-related adverse event.

*Not included in analyses; the values here were added from the safety table, calculated by summing study drug related toxicity + toxicity unrelated to treatment. "The most common reasons for treatment discontinuation were disease progression (17 [18%] of 94 patients in the combination group vs 19 [41%] of 46 in the ipilimumab group) and study drug toxicity (46 [49%] patients in the combination group vsten [22%] in the ipilimumab group)."

A13. Priority question: It is stated in the CS (Appendix D, Section D4.1.3) that to fit FP models "for each treatment arm of each study in the NMA, the reported Kaplan–Meier curves were digitised." Please provide references to the published K-M curves that were digitised and please explain why data were digitised from K-M curves for the RELATIVITY-047 and CheckMate-067 trials when patient level data were available.

Table 15 presented in the response to A12 details which references provided KM data that were digitized. Where required for each treatment arm of each study in the NMA, the reported KM curves were digitized using DigitizeIt® (http://www.digitizeit.de/).

Please note that IPD were used for RELATIVITY-047, for CheckMate-067 published KM curves were used. Digitized curves are cross-referenced against the reported survival data available in publications and/or the CSR (i.e. medians, HRs) to ensure that there is alignment in values that can be estimated from the digitized KM curve and the reported data values, and therefore utilising IPD from this trial would not be expected to change the results.

A14. Priority question: Please provide details of the statistical software and packages or statistical code used to conduct:

- **a) FP NMAs**
- **b) NMAs assuming constant HRs**
- **c) NMAs of binary safety and tolerability outcomes**
- **d) adjusted indirect treatment comparison (inverse probability treatment weights)**

For the NMA, the parameters of the different models were estimated using a Markov Chain Monte Carlo method implemented in the JAGS software program with the rjags package in R. The first series of iterations from the JAGS sampler was discarded as 'burn-in', and the inferences were based on additional iterations using two chains. All analyses were performed using R version 4.1.3 (http://www.r-project.org/) and JAGS version 4.3.0.

For the adjusted ITC, analyses were performed using R version 4.1.0 (http://www.r-project.org/)

A15. Priority question: Please assess inconsistency in the NMAs for all outcomes (see Technical Support Document 4 for details of methods).

It is acknowledged that there is a closed loop in the network of evidence (CS, Figure 7) but this is a result of a three-arm study (CheckMate-067), which by definition is

consistent. Thus, there are no closed loops in the NMA evidence network warranting a consistency assessment.

Adjusted indirect treatment comparisons (ITCs)

A16. Priority question: In relation to the company NMAs (CS, Section B.2.9.1), it is stated in the CS, Section B.2.9.1.3 that the "trials ultimately included in the SLR were considered homogeneous for suspected treatment effect modifiers" and in the CS, Appendix D, Section D.4.1.1.3, the company, in their feasibility assessment, identified no important differences in baseline characteristics between the RELATIVITY-047 and CheckMate-067 trials.

Please justify the rationale for conducting the adjusted ITC to "address imbalances in the distribution of baseline characteristics between patients from the RELATIVITY-047 and CheckMate-067 trials" (CS, Section B.2.9.2.1).

An NMA compares the treatment effects of interventions that have not been studied in head-to-head trials. In order to ensure that these indirect comparisons are not affected by differences in study effects between studies (i.e., known and unknown prognostic factors), the NMA considers only the relative treatment effects of each trial. In combining direct and indirect evidence in an NMA, trials must be considered reasonably similar. Specifically, there should be no differences in the distribution of effect modifiers between the trials being synthesized. An effect modifier is a variable that impacts the observed relative treatment effect of an intervention versus a control. An imbalance in the distribution of effect modifiers between studies comparing different interventions results in consistency violations and therefore biased indirect comparisons. To ensure it was appropriate to combine the identified trials in a NMA framework, a comprehensive feasibility assessment was conducted. The feasibility assessment included an exploration of the distribution of baseline patient characteristics both within and between trials to identify factors that may bias indirect estimates (i.e. identify effect modifiers). As stated above, the feasibility assessment concluded the trials were sufficiently similar to be synthesized in the NMA, and none were recommended for exclusion.

Importantly, the assessment that the trials (including the distribution of baseline characteristics) were sufficiently similar to be combined in an NMA framework does not necessitate that all baseline characteristics must be equally distributed between the trials - patients are randomized only within trials, not across trials, and the equal distribution of baseline characteristics is a feature of randomization. However, access to patient-level data in both trials meant that a different methodology could be applied for the indirect treatment comparison of nivolumab-relatlimab vs nivolumab + ipilimumab. Specifically, the application of inverse probability of treatment weighting to the individual patient level data from both trials enabled balance to be achieved on all variables measured at baseline for both trials, prior to the assessment of the relative treatment effect. The observed relative treatment effect could therefore not be attributed to confounding on any of these variables. That the nivolumab arms from both trials also performed similarly after adjustment by the propensity score further validates the strength of the methodology.

Importantly, both analytical frameworks (the adjusted ITC and NMA) generated consistent conclusions – that is, that nivolumab-relatlimab has similar efficacy to nivolumab + ipilimumab, with a more favourable safety profile.

A17. Priority question: It is stated in the CS (Section B.2.9.2.1) that: "In CheckMate-067, PFS per BICR data were only available from the February 2015 database lock (minimum 9 months follow up), as this was not the primary endpoint definition of PFS. Therefore, a comparison of PFS per BICR were included in the current adjusted analyses, but were utilised data from the October 2021 database lock of RELATIVITY-047 only (minimum follow-up 9 months)." Please clarify whether an adjusted ITC was conducted for PFS per BICR and if so, please provide the results.

As noted in CS Section B.2.9.2.1. an adjusted ITC was conducted for PFS per BICR, utilising data from the October 2021 database lock of RELATIVITY-047 (minimum follow up 9 months).

Figure 30 presents PFS by BICR after adjusting for baseline characteristics. Median PFS per BICR for nivolumab + ipilimumab and nivolumab-relatlimab was [redacted] months (95% CI = [redacted], [redacted]) and [redacted] months (95% CI = [redacted], [redacted]),

respectively after weighting. After weighting, nivolumab-relatlimab demonstrated similar hazard of progression or death (per BICR) as nivolumab + ipilimumab (HR = [redacted], 95% CI = [redacted], [redacted]).

It is important to note that PFS per IA showed similar hazard of progression or death for nivolumab-relatlimab than for nivolumab + ipilimumab (HR [redacted], 95% CI = [redacted], [redacted]), with this confidence interval spanning one. Figure 31 presents the PFS per IA after adjusting for baseline characteristics. Thus, it can be concluded that that efficacy is similar when PFS endpoint definitions are alternated, with non-significant treatment effects and point estimates equal to or similar to one with highly overlapping CIs for both evaluations.

Figure 30: PFS per BICR after weighting (ITT population) – RELATIVITY-047 October 2021 DBL

Key: CI, confidence interval; DBL, database lock; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Figure 31: PFS per IA after weighting (ITT population) - RELATIVITY-047 October 2021 DBL

Key: CI, confidence interval; DBL, database lock; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

A18. Priority question: The inverse probability of the treatment weighting approach requires an assumption of overlap (Technical Support Document 17, pp50-51). Please provide an assessment of the overlap assumption, before and after weighting, for the comparisons of nivolumab-relatlimab versus nivolumab+ipilimumab and versus nivolumab (RELATIVITY-047 trial and CheckMate-067 trial data).

An assessment of overlap is provided in the submitted Appendix Section D.4.2.2, with Figure 3 demonstrating very high levels of distribution overlap between the two treatments.

A19. Priority question: Please provide the numbers of patients excluded, with reasons, from the patient level data sets of the RELATIVITY-047 and CheckMate-067 trials before weighting.

Numbers of patients excluded from the patient level data sets of the RELATIVITY-047 and CheckMate-067 trials before weighting are presented in Table 17. Patients

were only excluded if they had missing values on any of the specified covariates. This resulted in the exclusion of very few patients from each treatment arm.

Table 17: Attrition table (adjusted indirect treatment comparison)

	Nivolumab-relatlimab (RELATIVITY-047) (n=355)	Nivolumab + ipilimumab (CheckMate-067) (n=314)
Analysis set*	[redacted]	[redacted]
Excluded	[redacted]	[redacted]

Note: *Analysis set includes a subset of patients with non-missing values on all covariates – age, sex, geographic region, time from advanced melanoma diagnosis until randomisation, prior adjuvant therapy, AJCC stage, melanoma subtype, ECOG, BRAF mutation status, LDH category. PD-L1 expression. These covariates were used in propensity score calculation.

A20. Priority question: Please provide plots of Schoenfeld residuals versus time, log cumulative hazards versus log time and results of the Grambsch-Therneau test for PFS and OS after weighting for the comparisons nivolumab-relatlimab versus nivolumab+ipilimumab and nivolumab-relatlimab versus nivolumab (RELATIVITY-047 and CheckMate-067 trial data).

The Schoenfeld residuals plot and log-log plot for PFS for nivolumab-relatlimab versus nivolumab + ipilimumab are shown in Figure 32 and Figure 33, respectively. As the weighted comparison did not compare nivolumab-relatlimab to nivolumab, the corresponding plots were not generated. Plots for the comparison of the two nivolumab arms are provided. For both outcomes and both treatment comparisons the plots demonstrate no visual violation of the proportional hazards assumption.

Figure 32: Schoenfeld residuals plot for PFS with nivolumab-relatlimab versus nivolumab + ipilimumab

Figure 33: Log-log plot for PFS of nivolumab-relatlimab versus nivolumab + ipilimumab

Key: Nivo + Ipi, nivolumab +ipilimumab; Nivo + rela, nivolumab-relatlimab.

The Schoenfeld residuals plot and log-log plot for PFS for the nivolumab arms of RELATIVITY-047 and CheckMate-067 are shown in Figure 34 and Figure 35, respectively.

Figure 34: Schoenfeld residuals plot for PFS with nivolumab (RELATIVITY-047) versus nivolumab (CheckMate-067)

Figure 35: Log-log plot for PFS with nivolumab (RELATIVITY-047) versus nivolumab (CheckMate-067)

Key: Nivo (047), nivolumab arm (RELATIVITY-047); Nivo (067), nivolumab arm (CheckMate-067).

The Schoenfeld residuals plot and log-log plot for PFS for the nivolumab arms of RELATIVITY-047 and CheckMate-067 are shown in Figure 36 and Figure 37, respectively.

Figure 36: Schoenfeld residuals plot for OS with nivolumab-relatlimab versus nivolumab + ipilimumab

Figure 37: Log-log plot for OS for the nivolumab (RELATIVITY-047) and nivolumab (CheckMate-067)

Key: Nivo + Ipi, nivolumab+ipilimumab; Nivo + Rela, nivolumab-relatlimab.

The Schoenfeld residuals plot and log-log plot for PFS for the nivolumab arms of RELATIVITY-047 and CheckMate-067 are shown in Figure 38 and

Figure 39, respectively.

Figure 38: Schoenfeld residuals plot for OS with nivolumab (RELATIVITY-047) versus nivolumab (CheckMate-067)

Figure 39: Log-log plot for OS for nivolumab (RELATIVITY-047) and nivolumab (CheckMate-67)

Key: Nivo (047), nivolumab arm (RELATIVITY-047); Nivo (067), nivolumab arm (CheckMate-067).

A21. Priority question: Please provide safety results for the weighted nivolumab arms in the adjusted ITC for the outcomes referred to in the CS (Section B.2.9.2.2.3).

A summary of any grade AEs within 28 months of follow-up from the nivolumab arms of RELATIVITY-047 and CheckMate-067 trials before and after weighting is presented in Table 18. Improvements in AE management over time may explain differences in observed rates between the trials.

Table 18: Summary of any grade AEs within 28 months of follow up[1] amongst patients in the nivolumab (RELATIVITY-047 trial) and nivolumab (CheckMate-067 trial) arms before and after application of IPT weighting[1]

	Unweighted		IPT-weighted[4]	
	Nivo (047) N = 354	Nivo (067) N = 303	Nivo (047) N = 338	Nivo (067) N = 287
SAEs[3]				
All-causality SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related SAEs	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to DC	[redacted]	[redacted]	[redacted]	[redacted]
All-causality AEs leading to DC	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related AEs leading to DC	[redacted]	[redacted]	[redacted]	[redacted]
AEs	[redacted]	[redacted]	[redacted]	[redacted]
All-causality AEs	[redacted]	[redacted]	[redacted]	[redacted]

Data sources: CheckMate 067 trial (database lock: November 12, 2021); RELATIVITY-047 trial (database lock: October 27, 2022)

Abbreviations:

AEs: adverse events, AJCC: American Joint Committee on Cancer, DC: discontinuation, ECOG PS: Eastern Cooperative Oncology Group Performance Status, IPT: inverse probability of treatment, LDH: lactate dehydrogenase, M: metastasis, Nivo: nivolumab, PD-L1: programmed cell death ligand 1, SAEs: serious adverse events, ULN: upper limit of normal, UTI: urinary tract infection.

Notes:

[1] All AEs are restricted to events occurring within 30 days of the last dose of study drug (i.e., treatment-emergent) during the first 28 months of follow up.

[2] IPT weights with stabilization and truncation at the 5th and 95th percentiles are used. The probability of treatment was estimated through binary logistic regression separately for Nivolumab-relatlimab vs. Nivolumab+ipilimumab and Nivolumab (047) vs. Nivolumab (067), and captures patients' probability of being included in the RELATIVITY-047 trial vs. the CheckMate 067 trial. Covariates in the model include age group (years), sex (female vs. male), geographic region (Rest of World vs. USA), time from advanced melanoma diagnosis until randomization (years), prior adjuvant therapy (yes vs. no), AJCC M stage with LDH category 1 (M1any[1] vs. M0/M1any[0]), AJCC disease stage (stage III vs. stage IV), melanoma subtype (acral vs. cutaneous; mucosal vs. cutaneous; other vs. cutaneous), ECOG PS (≥ 1 vs. 0), BRAF mutation status (positive vs. wild-type), LDH category 1 (> ULN vs. ≤ ULN), LDH category 2 (> 2 X ULN vs. ≤ 2 X ULN), and PD-L1 expression category (≥ 1% vs. < 1%/non-quantifiable). The sample includes a subset of patients with non-missing values on all covariates included in the binary logistic regression model.

[3] An SAE was defined in both the CheckMate 067 trial and the RELATIVITY-047 trial consistently as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event that may jeopardize the participant or may require intervention to prevent one of the other serious outcomes listed previously.

[4] N per arm reflects the effective sample size after weighting.

Section B: Clarification on cost effectiveness data

RELATIVITY-047 trial utility values

B1. Priority question: Please provide further details of the methods used to derive base case health state utility values. Please include an overview of the summary statistics considered, any plots produced to justify decisions influencing choice of statistical models, the approach to assessing and dealing with missing values, and the method used to calculate base case health state utility values.

The principal population for these analyses is the intention-to-treat (ITT) population from the RELATIVITY-047 trial October 2022 DBL. All ITT patients and visits were included regardless of availability of baseline and/or post-baseline questionnaires. Baseline responses were included in all analyses.

If there was only one assessment per visit, this record was selected. If more than one assessment was collected for a visit, the assessment closest to the planned visit day was selected. If two assessments were made at the same distance from the planned visit day, the latest assessment was selected. If two assessments were made on the same day, the earliest data entry was selected.

Records with a missing response on any EQ5D domains were removed from the analysis. Similarly, records with invalid responses were removed. Specifically, EQ5D domain responses were required to be a number in the set (1, 2, 3). No attempt was made to impute missing data.

The utility scores were calculated for multiple countries, based on individual value sets for each country. The formula used for the UK is outlined below. [7] For each formula MO indicates Mobility, SC indicates Self Care, UA indicates Usual Activities, PDI indicates Pain/Discomfort, and AD indicates Anxiety/Depression. The number following the codes indicates a level 2 or 3 response, i.e. moderate problems, or extreme problems, respectively.

$$EQ5D\ index = 1 - 0.081 * N2 - 0.069 * MO2 - 0.314 * MO3 - 0.104 * SC2 - 0.214 * SC3 - 0.036 * UA2 - 0.094 * UA3 - 0.123 * PDI2 - 0.386 * PDI3 - 0.071 * AD2 - 0.236 * AD3 - 0.269 * N3$$

The effect of disease progression and treatment status on HSUV was formally assessed using linear mixed effects models fitted to the full analysis set.

A subject ID random effect was included to reflect the fact that each patient provides multiple values. The following combinations of fixed effects were initially modelled:

- Progression status only (PD / PF)
- Progression status and treatment arm but no interaction (Progression status + Treatment arm)
- Progression status and treatment arm and their interaction (Progression status*treatment arm)
- Treatment status only (on Treatment / off Treatment)
- Treatment status and treatment arm but no interaction (Treatment status + treatment arm)
- Treatment status and treatment arm and their interaction (Treatment status*treatment arm)

For each model, coefficients estimated by the model are reported alongside standard errors, confidence intervals and p-values. In addition, Least Squares means, also known as predicted marginal means, were calculated for each model. For the three progression status models and the three treatment status models, goodness-of-fit statistics were calculated. In addition, a Likelihood Ratio test was conducted to determine the best-fitting model.

To explore the factors that predict country-specific EQ-5D-3L utility values, the mixed models were rerun with the inclusion of predictive factors. Alongside treatment arm, progression status and treatment status as included above, the magnitude and significance of the following fixed effects was evaluated:

- Age group (<65 / ≥65)
- Sex (male / female)

- Disease stage (M0/M1 [0] / M1 any [1])
- BRAF status (mutant / wild type / not reported)
- PD-L1 status (<1%/unknown / ≥1% OR positive / negative)
- LAG-3 (<1%/unknown / ≥1% OR positive / negative)
- Baseline LDH (≥ upper limit of normal / < upper limit of normal)
- Baseline ECOG performance status (0 / 1)

Different combinations of prognostic factor variables were assessed using the step function in R. This function automatically performs iterative removal of insignificant variables to determine the best-fitting combination of fixed effect variables. Treatment arm, progression status and treatment status fixed effects were always included in the base case regardless of significance. If the interaction variables estimated in the previous analysis were found to be significant then these were included as well.

For the best-fitting model, coefficients with confidence intervals and p-values were reported. Least Squares means were also estimated from this model for the primary variables of interest: progression status, treatment status and treatment arm.

Summary statistics for the EQ-5D-3L responses for the ITT population using the Dolan [7] value set for the United Kingdom are shown in Table 19. The summary statistics are provided across all visits, by progression status (progressed disease / progression-free) and treatment status (on treatment / off treatment).

The mean EQ-5D-3L across all visits is [redacted]. Mean utility is lower for progressed disease patients with [redacted] compared to [redacted] for progression-free. Patients on treatment overall had a higher utility of [redacted] compared to [redacted] for patients off treatment.

Table 19: Summary statistics for EQ-5D-3L utilities using the United Kingdom value set

	Overall			
	N	Mean (SD)	Median (IQR)	Min - Max
Total	[redacted]	[redacted]	[redacted]	[redacted]
Progression status				
PF	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status				
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment	[redacted]	[redacted]	[redacted]	[redacted]

Key: N = total number of assessments across all patients and visits; SD = Standard deviation; IQR = Interquartile range; Min = Minimum; Max = Maximum; PF = Progression-free; PD = Progressed disease

B2. Priority question: Please provide further results from the base case utility value analysis (CS, Table 43). Please present all outputs by:

- **progression status**
- **progression status by treatment arm**
- **treatment arm by treatment status**
- **progression status by treatment arm by treatment status**

Progression status models

The results of the mixed effects model including only a fixed effect for progression status alongside the random effect for subject id are shown in Table 20. The progressed disease state had a statistically significant lower utility ($p<0.0001$), but only marginally lower, with an estimated mean utility of [redacted] compared to [redacted] for the progression-free state.

Table 20: United Kingdom mixed effects model results for progression status

Parameter	Coefficient	Standard error	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Progression status				
PD	[redacted]	[redacted]	[redacted]	[redacted]

Key: PD = Progressed disease; PF = Progression-free; CI = confidence interval

The results of the mixed effects model including a fixed effect for treatment arm as well as the progression status fixed effect are shown in Table 21. Treatment arm is statistically insignificant (p = [redacted]) indicating no difference in utility for the two treatment arms. The estimated utilities for the progression status variables are unchanged following the inclusion of treatment arm.

Table 21: United Kingdom mixed effects model results for progression status + treatment arm

Parameter	Coefficient	Standard error	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Progression status				
PD	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm				
Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Key: PD = Progressed disease; PF = Progression-free; CI = confidence interval				

The results of the mixed effects model including a variable for the interaction between progression status and treatment arm are shown in Table 22. The interaction between progression status and treatment arm is statistically significant (p<[redacted]), whilst treatment arm remains statistically insignificant (p=[redacted]). However, the results from this model lack face validity, as they infer that patients who progression on nivolumab-relatlimab have an improved utility compared with patients on nivolumab-relatlimab who are progression-free. As such, these results were not used in the cost-effectiveness model.

Table 22: United Kingdom mixed effects model results for progression status*treatment arm

Parameter	Coefficient	Standard error	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Progression status				
PD	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm				
Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Progression status: Treatment arm				
PD: Relatlimab	[redacted]	[redacted]	[redacted]	[redacted]

+ nivolumab				
Key: PD = Progressed disease; PF = Progression-free; CI = confidence interval				

The results of the likelihood ratio test are given in Table 23. The best-fitting model based on the AIC is the model that includes fixed effects for progression status, treatment arm and the interaction between progression status and treatment arm. This is confirmed by the likelihood ratio test, with a p-value < [redacted] for the inclusion of the interaction variable. However, as noted, this model lacks face validity. Of the remaining two models, the inclusion of treatment arm has a coefficient of zero, indicating that this does not contribute to predictive performance. This is confirmed by the non-significant p-value ([redacted]). Hence the model with just progression status is used in the cost-effectiveness model.

Table 23: Likelihood ratio test for United Kingdom progression status models

Model	AIC	BIC	logLik	Chisq	Df	p.value
Progression status	[redacted]	[redacted]	[redacted]			
Progression status + treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression status*treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; logLik = log-Likelihood; Chisq = Chi-squared; Df = Degrees-of-freedom						

Treatment status models

The results of the mixed effects model including only a fixed effect for treatment status alongside the random effect for subject ID are shown in Table 24. Patients on treatment had a statistically significant higher estimated utility of [redacted] compared to [redacted] for patients off treatment (p< [redacted]).

Table 24: United Kingdom mixed effects model results for treatment status

Parameter	Coefficient	Standard error	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status				
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI = confidence interval				

The results of the mixed effects model including a fixed effect for treatment arm as well as the treatment status fixed effect are shown in Table 25. Treatment arm is statistically insignificant (p = [redacted]) indicating no difference in utility for the two treatment arms. The estimated utilities for the treatment status variables are unchanged following the inclusion of treatment arm.

Table 25: United Kingdom mixed effects model results for treatment status + treatment arm

Parameter	Coefficient	Standard error	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status				
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm				
Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI = confidence interval				

The results of the mixed effects model including a variable for the interaction between treatment status and treatment arm are shown in Table 26. The interaction between treatment status and treatment arm is statistically significant (p<[redacted]), and treatment arm is now also statistically significant at the 5% level (p = [redacted]). However, as with the analysis by progression status, the model including an interaction term lacks face validity. In this instance, it suggests that treatment allocation will influence a patient's utility value even when they are not on treatment of the two treatment arms, patients who were randomised to nivolumab-relatlimab have an increase in utility of [redacted] when not on treatment; this is almost double the utility benefit of remaining progression-free ([redacted]).

Table 26: United Kingdom mixed effects model results for treatment status*treatment arm

Parameter	Coefficient	Standard error	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status				
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Treatment arm				
Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status: Treatment arm				
On treatment: Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Key: CI = confidence interval				

The results of the likelihood ratio test are given in Table 27. The best-fitting model based on the AIC is the model that includes fixed effects for treatment status, treatment arm and the interaction between treatment status and treatment arm. This is confirmed by the likelihood ratio test, with p<[redacted] for the inclusion of the interaction variable.

Table 27: Likelihood ratio test for United Kingdom treatment status models

Model	AIC	BIC	logLik	Chisq	Df	p.value
Treatment status	[redacted]	[redacted]	[redacted]			
Treatment status + treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status*treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; logLik = log-Likelihood; Chisq = Chi-squared; Df = Degrees-of-freedom						

The results of the mixed effects model including fixed effects for baseline characteristics are shown in Table 28. The baseline characteristics (excluding progression status, treatment status and treatment arm) were selected based on iterative removal of statistically insignificant variables, so that only statistically significant fixed effects were retained. Progression status, treatment status and treatment arm were always included in the mixed effects model, regardless of significance. The results show that of these variables, only treatment arm was

statistically insignificant suggesting no difference in utility between the two treatment arms (p=[redacted]).

Statistically significantly lower utility was associated with progressed disease, being off treatment, being younger (<65 years old), being female, having an M1 disease stage, negative LAG-3 and baseline ECOG performance status equal to 1.

The corresponding Least Squares mean estimates for progression status, treatment status and treatment arm are given in Table 29. Estimated utility for both progressed disease and progression-free patients is lower after controlling for baseline characteristics. Utility for progressed disease individuals has fallen from [redacted] to [redacted], and for progression-free individuals it has fallen from [redacted] to [redacted]. Similarly, for treatment status, on treatment utility has fallen from [redacted] to [redacted] after controlling for baseline characteristics and off treatment utility has fallen from [redacted] to [redacted].

Table 28: United Kingdom mixed effects model results including baseline characteristics

Parameter	Coefficient	Standard error	95% CI	P-value
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
Progression status				
PD	[redacted]	[redacted]	[redacted]	[redacted]
PF				
Treatment				
Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Treatment status				
On treatment	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment				
Age				
<65	[redacted]	[redacted]	[redacted]	[redacted]
>=65				
Sex				
Female	[redacted]	[redacted]	[redacted]	[redacted]
Male				
Disease stage				
M0/M1any [0]	[redacted]	[redacted]	[redacted]	[redacted]
M1 any [1]				
LAG-3				
Negative	[redacted]	[redacted]	[redacted]	[redacted]
Positive				
Baseline ECOG				

performance status				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]			
Progression status:Treatment arm				
PD:Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
PF:Nivolumab	[redacted]			
Treatment status: Treatment arm				
On treatment: Relatlimab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Off treatment:Nivolumab	[redacted]			
Key: PD = Progressed disease; PF = Progression-free; ECOG = Eastern Cooperative Oncology Group; LAG-3 = lymphocyte-activation gene 3; M = metastasis; CI = confidence interval				

Table 29: United Kingdom Least Squares mean estimates for progression status, treatment status and treatment arm variables, from the mixed effects model including baseline characteristics

Level	Estimated mean	95% CI	P-value
PD	[redacted]	[redacted]	[redacted]
PF	[redacted]	[redacted]	[redacted]
Relatlimab + Nivolumab	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
PD:Relatlimab + Nivolumab	[redacted]	[redacted]	[redacted]
PF:Relatlimab + Nivolumab	[redacted]	[redacted]	[redacted]
PD:Nivolumab	[redacted]	[redacted]	[redacted]
PF:Nivolumab	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]
Off treatment	[redacted]	[redacted]	[redacted]
Relatlimab + Nivolumab:On treatment	[redacted]	[redacted]	[redacted]
Nivolumab:On treatment	[redacted]	[redacted]	[redacted]
Relatlimab + Nivolumab:Off treatment	[redacted]	[redacted]	[redacted]
Nivolumab:Off treatment	[redacted]	[redacted]	[redacted]

Key: PD = Progressed disease; PF = Progression-free; CI = confidence interval

A likelihood ratio test was performed for the models with and without the treatment arm, progression status, treatment status and interaction variables, but including baseline covariates. The results of this are shown in Table 30 and demonstrate that the inclusion of treatment arm is statistically insignificant (p=[redacted]) once baseline characteristics have been controlled for but the inclusion of both interaction variables for progression status with treatment arm and treatment status with treatment arm are statistically significant (p<[redacted]).

Table 30: Likelihood ratio test for models including baseline characteristics

Model	AIC	BIC	logLik	Chisq	Df	p.value
Progression status + treatment status + covariates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ treatment arm + progression status:treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+ treatment arm + progression status:treatment arm + treatment status:treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; logLik = log-Likelihood; Chisq = Chi-squared; Df = Degrees-of-freedom

Please present the following results

a) **calculated mean utility value and SE at each questionnaire time point**

b) **overall mean utility value and SE**

c) **number of respondents at each questionnaire time point**

d) **number of missing values at each questionnaire time point**

The overall mean utility value and SE and number of respondents at each visit is provided in Table 31. Results are provided by treatment arm and for the full ITT population. The mean utility at each time point varies between [redacted] and [redacted] in the nivolumab-relatlimab arm, and between [redacted] and [redacted] in the nivolumab arm.

Table 31: Mean EQ-5D utility by visit - UK value set

	Nivolumab + Relatlimab		Nivolumab		Overall	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
BASELINE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 52	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 68	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 76	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 104	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

WEEK 108	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 112	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 116	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 120	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 124	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 128	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 132	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 136	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 140	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 144	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 148	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 152	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 156	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 160	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 164	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 168	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 172	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 176	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 180	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 184	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 188	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 192	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 196	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 204	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 208	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 212	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 216	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 220	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLLOW-UP 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SURVIVAL FOLLOW-UP 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURVIVAL FOLLOW-UP 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The completion rates for the EQ-5D-3L questionnaire for the ITT population are shown in Table 32 for each visit number. The completion rate is defined as the number of complete and valid questionnaires out of the number of patients in the study for that visit. The responses for the completed questionnaires listed here are the responses used in the later analyses. For the initial visits, up to week 220, the completion rates were high, mostly above [redacted]%. For the follow-up visits, however, the completion rates fell to approximately [redacted]%.

Table 32: Completion rates for the EQ-5D-3L questionnaire

	Completion rate	
Visit	Relatlimab + Nivolumab	Nivolumab

BASELINE		[redacted]			[redacted]	
WEEK 4		[redacted]			[redacted]	
WEEK 8		[redacted]			[redacted]	
WEEK 12		[redacted]			[redacted]	
WEEK 16		[redacted]			[redacted]	
WEEK 20		[redacted]			[redacted]	
WEEK 24		[redacted]			[redacted]	
WEEK 28		[redacted]			[redacted]	
WEEK 32		[redacted]			[redacted]	
WEEK 36		[redacted]			[redacted]	
WEEK 40		[redacted]			[redacted]	
WEEK 44		[redacted]			[redacted]	
WEEK 48		[redacted]			[redacted]	
WEEK 52		[redacted]			[redacted]	
WEEK 56		[redacted]			[redacted]	
WEEK 60		[redacted]			[redacted]	
WEEK 64		[redacted]			[redacted]	
WEEK 68		[redacted]			[redacted]	
WEEK 72		[redacted]			[redacted]	
WEEK 76		[redacted]			[redacted]	
WEEK 80		[redacted]			[redacted]	
WEEK 84		[redacted]			[redacted]	
WEEK 88		[redacted]			[redacted]	
WEEK 92		[redacted]			[redacted]	
WEEK 96		[redacted]			[redacted]	
WEEK 100		[redacted]			[redacted]	
WEEK 104		[redacted]			[redacted]	
WEEK 108		[redacted]			[redacted]	
WEEK 112		[redacted]			[redacted]	
WEEK 116		[redacted]			[redacted]	
WEEK 120		[redacted]			[redacted]	
WEEK 124		[redacted]			[redacted]	
WEEK 128		[redacted]			[redacted]	
WEEK 132		[redacted]			[redacted]	
WEEK 136		[redacted]			[redacted]	
WEEK 140		[redacted]			[redacted]	
WEEK 144		[redacted]			[redacted]	
WEEK 148		[redacted]			[redacted]	
WEEK 152		[redacted]			[redacted]	
WEEK 156		[redacted]			[redacted]	
WEEK 160		[redacted]			[redacted]	
WEEK 164		[redacted]			[redacted]	
WEEK 168		[redacted]			[redacted]	
WEEK 172		[redacted]			[redacted]	
WEEK 176		[redacted]			[redacted]	
WEEK 180		[redacted]			[redacted]	
WEEK 184		[redacted]			[redacted]	

WEEK 188	[redacted]		[redacted]	
WEEK 192				
WEEK 196				
WEEK 200				
WEEK 204				
WEEK 208				
WEEK 212				
WEEK 216				
WEEK 220				
FOLLOW-UP 1				
FOLLOW-UP 2				
SURVIVAL FOLLOW-UP 1				
SURVIVAL FOLLOW-UP 2				
SURVIVAL FOLLOW-UP 3				
SURVIVAL FOLLOW-UP 4				
SURVIVAL FOLLOW-UP 5				
SURVIVAL FOLLOW-UP 6				
SURVIVAL FOLLOW-UP 7				
SURVIVAL FOLLOW-UP 8				
SURVIVAL FOLLOW-UP 9				
SURVIVAL FOLLOW-UP 10				
SURVIVAL FOLLOW-UP 11				
SURVIVAL FOLLOW-UP 12				
SURVIVAL FOLLOW-UP 13				
SURVIVAL FOLLOW-UP 14				
SURVIVAL FOLLOW-UP 15				

Some of the questionnaire responses were removed due to being either incomplete or invalid. Incomplete questionnaires were those with any missing responses to the 5 questions of the EQ-5D-3L. Questionnaires with missing responses to the VAS questionnaire were still included. Invalid questionnaires were any questionnaires with responses not equal to either 1, 2 or 3. The number of incomplete or invalid questionnaires at each visit out of the number of responses for each visit are shown in Table 33. There were very few invalid or incomplete responses, with most visits having no responses removed. For visits with incomplete or invalid responses, these only had a maximum of three responses removed.

Table 33: Number of incomplete or invalid EQ-5D-3L questionnaires

	Incomplete / invalid responses			
Visit	Relatlimab + Nivolumab		Nivolumab	
BASELINE	[redacted]		[redacted]	
WEEK 4				

WEEK 8				
WEEK 12				
WEEK 16				
WEEK 20				
WEEK 24				
WEEK 28				
WEEK 32				
WEEK 36				
WEEK 40				
WEEK 44				
WEEK 48				
WEEK 52				
WEEK 56				
WEEK 60				
WEEK 64				
WEEK 68				
WEEK 72				
WEEK 76				
WEEK 80				
WEEK 84				
WEEK 88				
WEEK 92				
WEEK 96				
WEEK 100				
WEEK 104				
WEEK 108				
WEEK 112				
WEEK 116				
WEEK 120				
WEEK 124				
WEEK 128				
WEEK 132				
WEEK 136				
WEEK 140				
WEEK 144				
WEEK 148				
WEEK 152				
WEEK 156				
WEEK 160				
WEEK 164				
WEEK 168				
WEEK 172				
WEEK 176				
WEEK 180				
WEEK 184				
WEEK 188				
WEEK 192				

WEEK 196	[redacted]			[redacted]	
WEEK 200					
WEEK 204					
WEEK 208					
WEEK 212					
WEEK 216					
WEEK 220					
FOLLOW-UP 1					
FOLLOW-UP 2					
SURVIVAL FOLLOW-UP 1					
SURVIVAL FOLLOW-UP 2					
SURVIVAL FOLLOW-UP 3					
SURVIVAL FOLLOW-UP 4					
SURVIVAL FOLLOW-UP 5					
SURVIVAL FOLLOW-UP 6					
SURVIVAL FOLLOW-UP 7					
SURVIVAL FOLLOW-UP 8					
SURVIVAL FOLLOW-UP 9					
SURVIVAL FOLLOW-UP 10					
SURVIVAL FOLLOW-UP 11					
SURVIVAL FOLLOW-UP 12					
SURVIVAL FOLLOW-UP 13					
SURVIVAL FOLLOW-UP 14					
SURVIVAL FOLLOW-UP 15					

Section C: Textual clarification and additional points

Company submission documents

C1. Priority question: There is a comment to 'update page numbers quoted in all sections of Doc A once Doc B has been finalised' in CS Document A. When all fields in this document are updated, there are 26 'Error! Reference source not found' messages and the page numbering changes. Please provide an updated version of CS Document A with the correct references and correct table, figure and page numbering (i.e., with all fields in the document updated).

Please refer to Document A embedded as a file below/provided in the reference pack for this document.

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A_Document A _28042

C2. Priority question: The EAG was unable to open the embedded Word document for the draft SmPC in CS, Appendix C. Please clarify whether the embedded draft SmPC document is the same as the CS Document B PDF reference '8. BMS-2023-Draft SmPC.pdf'. If this differs, please explain why and provide the embedded Word document separately.

We can confirm the embedded draft SmPC is the same as that provided in the reference pack (Ref.8 of CS Document B).

RELATIVITY-047 trial safety and tolerability results

C3. The source of information presented in CS, Table 19 is reported as the RELATIVITY-047 CSR addendum 2 (October 2022 data-cut). However, the number of patients who experienced any Grade 3-4 AEs and the number of patients who experienced any Grade 3-4 serious AEs (SAEs) reported in this table do not match the number reported in RELATIVITY-047 CSR addendum 2 (October 2022 data-cut), Table 8.1-1 Please explain this inconsistency.

Thank you for bringing this inconsistency to our attention. Please use the following data, as per the RELATIVITY-047 CSR addendum 2 (Table 8.1-1, pages 56-57).

Table 34: Summary of AEs (ITT population)

	Nivolumab-relatlimab (n = 355)		Nivolumab (n = 359)	
	Any Grade	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Any AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs, n (%)				
SAEs, n (%)				
TRSAEs, n (%)				
AEs leading to discontinuation, n (%)				
TRAEs leading to discontinuation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; ITT, intention-to-treat; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.
Source: RELATIVITY-047 CSR addendum 2 (October 2022 data-cut)[10]

C4. The source for CS, Table 20 is reported as RELATIVITY-047 CSR addendum 2 (October 2022 data-cut). However, the number of patients who experienced some AEs (treatment-related asthenia, nausea, alanine aminotransferase increased, aspartate transaminase increased, myalgia, decreased appetite, hyperthyroidism and infusion-related reactions) is not reported in RELATIVITY-047 CSR addendum 2 (October 2022 data-cut), Table 8.1-1. Please explain this inconsistency and provide the correct source.

Please refer to the RELATIVITY-047 CSR addendum 2 supplementary tables (Table S.6.1.32.1) embedded below/provided in the reference pack for this document. This data was not previously provided in the reference pack.

[redacted]

C5. In the draft nivolumab-ipilimumab SmPC (Section 4.8, p10), higher proportions of patients were reported to have experienced the most common AEs and the most common serious AEs than were reported in RELATIVITY-047 CSR addendum 2 (October 2022 data- cut), Table 8.1-1. Please explain this inconsistency and provide the results from the most recent data-cut.

Please noted that the inconsistencies highlighted are related to the regulatory process for filing. For the SmPC, special analyses are required where AE frequencies are reported with a) the AE terms associated with disease progression removed and, b) where MedDRA PTs representing similar conditions are remapped programmatically. Hence, the differences in the SmPC frequencies compared to those reported in the CSR. Also please note, the SmPC is based on an earlier database lock (October 2021) than that of CSR addendum 2.

C6. Please clarify whether in CS, Document B, Table 21: Endocrine and non-endocrine immune-mediated adverse event summary by worst CTCAE grade (ITT population), the number of patients who experienced 'Hypothyroidism' or 'Thyroiditis' are also included in the number of patients who experienced 'Hypothyroidism/thyroiditis'.

Table 35 presents the number of patients who experienced hypothyroidism, thyroiditis, and hypothyroidism/thyroiditis (i.e., hypothyroidism and/or thyroiditis). Please note there is a minor typo in the CS; the number of patients who experienced any grade hypothyroidism/thyroiditis in the nivolumab-relatlimab is [redacted] ([redacted]).[5]

Table 35: Endocrine immune-mediated adverse event summary by worst CTCAE grade (ITT population)

	Nivolumab-relatlimab (n = 355)			Nivolumab (n = 359)		
	Any Grade	Grade 3–4	Grade 5	Any Grade	Grade 3–4	Grade 5
Endocrine immune-mediated adverse events						

Hypothyroidism/thyroiditis	[redacted]
Hypothyroidism	
Thyroiditis	
Source: RELATIVITY-047 CSR addendum 02 supplementary tables[5]	

Indirect treatment comparison and NMA

C7. It is stated in the CS (Appendix D, Section D4.1.3) that the first step used when selecting time-varying NMA models was to "Run full and less complex fractional polynomial models for all combinations of P1 and P2". Please clarify what the phrase 'full and less complex fractional polynomial models' means.

A variety of fractional polynomial NMA models were explored. This included simpler 1st order FP models (2 parameters), as well as more complicated 2nd order FP models (3 parameters) which included NMA models with treatment effects on the scale + 1st shape and treatment effects on the scale + 2nd shape.

C8. Please explain how the threshold of SMD<0.2, used to indicate sufficient balance between the two treatment groups after weighting, was selected (CS, Section B.2.9.2.1).

The choice of SMD < 0.2 was informed by the below paper:

Stuart EA. Matching methods for causal inference: A review and a look forward. Statistical science: a review journal of the Institute of Mathematical Statistics. 2010

This paper recommends SMD < 0.25, hence to ensure a conservative approach, a value of 0.2 was used.

C9. Please provide the effective sample sizes of the nivolumab arms of the RELATIVITY-047 and the CheckMate-067 trials after weighting (CS, Appendix D, Table 19).

After weighting the sample size of the nivolumab arm of RELATIVITY-047 is [redacted], the effective sample size of the nivolumab arm of CheckMate-067 is [redacted].

Review methods

C10. Please provide the search strategies used to identify cost effectiveness studies (CS, Appendix G.1) and HRQoL studies (CS, Appendix H.1).

The searches run to identify results from APA PsycInfo®, EconLit, Embase®, MEDLINE® using ProQuest are outlined in Table 36 and Table 37.

Table 36: Search strategy for Embase, Medline, PsycInfo and EconLit via ProQuest (January 2022)

Set#	Searched for	Results
S1	TI,AB(melanoma)	309740*
S2	TI,AB(melanomalignoma OR melanocarcinoma)	177°
S3	EMB.EXACT("metastatic melanoma")	15809*
S4	EMB.EXACT(melanoma)	162571*
S5	MESH.EXACT(melanoma)	91236*
S6	S1 OR S2 OR S3 OR S4 OR S5	366099*
S7	EMB.EXACT("Cost effectiveness analysis")	170495*
S8	MESH.EXACT("Cost-benefit analysis")	93336*
S9	MESH.EXACT("Economics")	466673*
S10	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	161435*
S11	TI(cost NEAR/1 effectiveness)	63774*
S12	EMB.EXACT("Cost benefit analysis")	92573*
S13	EMB.EXACT("Economic aspect")	129051*
S14	EMB.EXACT("Socioeconomics")	160661*
S15	MESH.EXACT("Economics, pharmaceutical")	3042°
S16	EMB.EXACT("Health economics")	41458*
S17	MESH.EXACT("Costs and cost analysis")	52164*
S18	MESH.EXACT("Value of life")	6279*
S19	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1452004*
S20	TI,AB,IF(monte carlo)	143491*
S21	EMB.EXACT("Probability")	137993*
S22	MESH.EXACT("Decision Theory" OR "Decision Trees")	13476*
S23	EMB.EXACT("Decision Tree")	17476*
S24	MESH.EXACT("Markov chains")	16292*
S25	EMB.EXACT("Statistical Model")	200559*
S26	MESH.EXACT("Monte carlo method")	31654*
S27	EMB.EXACT("Decision Theory")	2834°
S28	EMB.EXACT("Monte carlo method")	46783*
S29	TI,AB,IF(markov)	79657*
S30	AB,IF(cost* NEAR/2 (effective* or utilit* or	695477*

	benefit* or minimi* or analy* or outcome or outcomes))	
S31	TI,AB,IF(value NEAR/2 (money or monetary))	10905*
S32	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	135325*
S33	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2700605*
S34	MESH.EXACT.EXPLODE("Costs and cost analysis")	269597*
S35	EMB.EXACT("Economics")	251580*
S36	EMB.EXACT("Cost")	65034*
S37	AB,IF(economic model*)	258732*
S38	MESH.EXACT("Models, economic")	11678*
S39	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38	4522997*
S40	S6 AND S39	7683*
S41	MESH.EXACT("Economics")	466673*
S42	EMB.EXACT("Economic aspect")	129051*
S43	EMB.EXACT("Socioeconomics")	160661*
S44	MESH.EXACT("Economics, pharmaceutical")	3042°
S45	EMB.EXACT("Health economics")	41458*
S46	MESH.EXACT("Costs and cost analysis")	52164*
S47	MESH.EXACT("Value of life")	6279*
S48	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1452004*
S49	MESH.EXACT("Hospital costs")	11989*
S50	MESH.EXACT("Employer health costs")	1097°
S51	MESH.EXACT("Cost savings")	12921*
S52	MESH.EXACT("Direct service costs")	1214°
S53	EMB.EXACT("Financial management")	125178*
S54	EMB.EXACT("Health care financing")	14115*
S55	MESH.EXACT.EXPLODE("Budgets")	14274*
S56	MESH.EXACT.EXPLODE("Economics, medical")	14623*
S57	TI,AB(Low NEAR/1 cost)	235989*
S58	MESH.EXACT("Drug costs")	17782*
S59	MESH.EXACT("Deductibles and Coinsurance")	1810°
S60	EMB.EXACT("Health care cost")	210774*
S61	MESH.EXACT("Health expenditures")	23938*

S62	TI,AB(Cost NEAR/1 variable)	5027*
S63	EMB.EXACT("Cost of illness")	21025*
S64	MESH.EXACT("Capital expenditures")	1997°
S65	MESH.EXACT("Cost allocation")	2020°
S66	EMB.EXACT("Hospital cost")	24562*
S67	MESH.EXACT("Cost control")	22355*
S68	MESH.EXACT.EXPLODE("Economics, hospital")	25886*
S69	MESH.EXACT("Cost sharing")	2645°
S70	MESH.EXACT("Cost of illness")	35474*
S71	TI,AB((Healthcare OR health*care) NEAR/1 cost*)	44936*
S72	TI,AB(Fiscal OR funding OR financial OR finance)	710350*
S73	MESH.EXACT.EXPLODE("Fees and charges")	34514*
S74	EMB.EXACT("Cost minimization analysis")	3865°
S75	TI,AB(Cost NEAR/1 estimate*)	48992*
S76	MESH.EXACT("Health care costs")	45946*
S77	MESH.EXACT("Economics, Nursing")	3982°
S78	MESH.EXACT("Medical savings accounts")	541°
S79	EMB.EXACT("Cost control")	76231*
S80	TI,AB(High NEAR/1 cost)	133955*
S81	TI,AB(Unit NEAR/1 cost*)	13372*
S82	TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2700605*
S83	MESH.EXACT.EXPLODE("Costs and cost analysis")	269597*
S84	EMB.EXACT("Economics")	251580*
S85	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84	4299554*
S86	S6 AND S85	6851*
S87	S40 OR S86	9857*
S88	TI,AB(case NEAR/1 (stud* OR report))	2136049*
S89	EMB.EXACT("Case study")	139388*
S90	EMB.EXACT("Abstract report" OR "Letter")	1226799*
S91	RTYPE("Case reports")	2240455*
S92	RTYPE("Letter")	2400935*

S93	RTYPE("Historical article")	367229*
S94	PSTYPE("Conference proceedings") AND PD(<20190101)	4327°
S95	DTYPE("Conference review") OR DTYPE("Conference abstract") OR DTYPE("Conference Paper") OR RTYPE("Conference abstract") AND PD(<20190101)	5090832*
S96	RTYPE("Editorial")	1354263*
S97	RTYPE("Note")	881573*
S98	S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97	13659970*
S99	S87 NOT S98	6462*
S100	S99 AND LA(english)	6169*
S101	advanced OR unresect* OR malign* OR metastat*	4132646*
S102	S100 AND S101	2005°

* Duplicates are removed from the search, but included in the result count.
° Duplicates are removed from the search and from the result count.

Table 37: Search strategy for Embase, Medline, PsycInfo and EconLit via ProQuest (November 2022)

Set#	Searched for	Results
S1	TI,AB(melanoma)	323670*
S2	TI,AB(melanomalignoma OR melanocarcinoma)	177°
S3	EMB.EXACT("metastatic melanoma")	16935*
S4	EMB.EXACT(melanoma)	170589*
S5	MESH.EXACT(melanoma)	94989*
S6	S1 OR S2 OR S3 OR S4 OR S5	383075*
S7	EMB.EXACT("Cost effectiveness analysis")	178188*
S8	MESH.EXACT("Cost-benefit analysis")	96400*
S9	MESH.EXACT("Economics")	468424*
S10	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	171079*
S11	TI(cost NEAR/1 effectiveness)	67344*
S12	EMB.EXACT("Cost benefit analysis")	95350*
S13	EMB.EXACT("Economic aspect")	132540*
S14	EMB.EXACT("Socioeconomics")	166261*
S15	MESH.EXACT("Economics, pharmaceutical")	3079°
S16	EMB.EXACT("Health economics")	42330*
S17	MESH.EXACT("Costs and cost analysis")	52817*
S18	MESH.EXACT("Value of life")	6295*
S19	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1539302*
S20	TI,AB,IF(monte carlo)	151034*
S21	EMB.EXACT("Probability")	147027*
S22	MESH.EXACT("Decision Theory" OR "Decision Trees")	13693*

S23	EMB.EXACT("Decision Tree")	19801*
S24	MESH.EXACT("Markov chains")	16616*
S25	EMB.EXACT("Statistical Model")	203055*
S26	MESH.EXACT("Monte carlo method")	32634*
S27	EMB.EXACT("Decision Theory")	2840°
S28	EMB.EXACT("Monte carlo method")	49472*
S29	TI,AB,IF(markov)	84586*
S30	AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))	732420*
S31	TI,AB,IF(value NEAR/2 (money or monetary))	11476*
S32	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	148011*
S33	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2805903*
S34	MESH.EXACT.EXPLODE("Costs and cost analysis")	277652*
S35	EMB.EXACT("Economics")	251978*
S36	EMB.EXACT("Cost")	66225*
S37	AB,IF(economic model*)	278122*
S38	MESH.EXACT("Models, economic")	11825*
S39	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38	4729982*
S40	S6 AND S39	8287*
S41	MESH.EXACT("Economics")	468424*
S42	EMB.EXACT("Economic aspect")	132540*
S43	EMB.EXACT("Socioeconomics")	166261*
S44	MESH.EXACT("Economics, pharmaceutical")	3079°
S45	EMB.EXACT("Health economics")	42330*
S46	MESH.EXACT("Costs and cost analysis")	52817*
S47	MESH.EXACT("Value of life")	6295*
S48	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1539302*
S49	MESH.EXACT("Hospital costs")	12142*
S50	MESH.EXACT("Employer health costs")	1097°
S51	MESH.EXACT("Cost savings")	13085*
S52	MESH.EXACT("Direct service costs")	1216°
S53	EMB.EXACT("Financial management")	127564*
S54	EMB.EXACT("Health care financing")	14275*
S55	MESH.EXACT.EXPLODE("Budgets")	14375*
S56	MESH.EXACT.EXPLODE("Economics, medical")	14676*
S57	TI,AB(Low NEAR/1 cost)	257863*

S58	MESH.EXACT("Drug costs")	18058*
S59	MESH.EXACT("Deductibles and Coinsurance")	1836°
S60	EMB.EXACT("Health care cost")	221379*
S61	MESH.EXACT("Health expenditures")	24914*
S62	TI,AB(Cost NEAR/1 variable)	5261*
S63	EMB.EXACT("Cost of illness")	21452*
S64	MESH.EXACT("Capital expenditures")	2000°
S65	MESH.EXACT("Cost allocation")	2025°
S66	EMB.EXACT("Hospital cost")	25582*
S67	MESH.EXACT("Cost control")	22378*
S68	MESH.EXACT.EXPLODE("Economics, hospital")	26069*
S69	MESH.EXACT("Cost sharing")	2698°
S70	MESH.EXACT("Cost of illness")	36381*
S71	TI,AB((Healthcare OR health*care) NEAR/1 cost*)	48911*
S72	TI,AB(Fiscal OR funding OR financial OR finance)	762816*
S73	MESH.EXACT.EXPLODE("Fees and charges")	34728*
S74	EMB.EXACT("Cost minimization analysis")	3969°
S75	TI,AB(Cost NEAR/1 estimate*)	51661*
S76	MESH.EXACT("Health care costs")	46854*
S77	MESH.EXACT("Economics, Nursing")	3983°
S78	MESH.EXACT("Medical savings accounts")	545°
S79	EMB.EXACT("Cost control")	78283*
S80	TI,AB(High NEAR/1 cost)	145028*
S81	TI,AB(Unit NEAR/1 cost*)	14040*
S82	TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2805903*
S83	MESH.EXACT.EXPLODE("Costs and cost analysis")	277652*
S84	EMB.EXACT("Economics")	251978*
S85	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84	4510188*
S86	S6 AND S85	7436*
S87	S40 OR S86	10656*
S88	TI,AB(case NEAR/1 (stud* OR report))	2256769*
S89	EMB.EXACT("Case study")	145009*
S90	EMB.EXACT("Abstract report" OR "Letter")	1261715*
S91	RTYPE("Case reports")	2301256*
S92	RTYPE("Letter")	2473166*

S93	RTYPE("Historical article")	368858*
S94	PSTYPE("Conference proceedings") AND PD(<20190101)	4327°
S95	DTYPE("Conference review") OR DTYPE("Conference abstract") OR DTYPE("Conference Paper") OR RTYPE("Conference abstract") AND PD(<20190101)	5379164*
S96	RTYPE("Editorial")	1415372*
S97	RTYPE("Note")	915641*
S98	S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97	14249486*
S99	S87 NOT S98	6903*
S100	S99 AND LA(english)	6607*
S101	advanced OR unresect* OR malign* OR metastat*	4419093*
S102	S100 AND S101	2165°
* Duplicates are removed from the search, but included in the result count. ° Duplicates are removed from the search and from the result count.		

The search strategy for the National Health Service Economic Evaluation Database via the Centre for Reviews and Dissemination search engine is presented in Table 38. This search strategy was used to identify records for the economic and HRQoL SLRs.

Table 38: NHS EED and HTA search strategy

Search type	Search string	CRD database	Hits
Title	“Advanced melanoma”; “metastatic melanoma “AND/OR “unresectable melanoma”	NHS EED	49
Title	“Advanced melanoma”; “metastatic melanoma “AND/OR “unresectable melanoma”	HTA	135
Total			184
Key: CRD = Centre for Reviews and Dissemination; NHS EED = The NHS Economic Evaluation Database; HTA = health technology assessment.			

The search strategy for the hand search of the NICE website for HTA submissions is presented in Table 39. This search strategy was used to identify records for the economic and HRQoL SLRs.

Table 39: NICE website searches

HTA	Search terms	Hits
NICE	"Advanced melanoma"; "metastatic melanoma "AND/OR "unresectable melanoma"	39

Key:NICE = National Institute for Health and Care Excellence.

The search strategies used to identify HRQoL studies in the original SLR and the November 2022 update are presented in Table 40 and Table 41.

Table 40: HRQoL Search Strategy for Embase, Medline, PsycInfo, and Econlit in ProQuest (24 January 2022)

Set#	Searched for	Results
S1	TI,AB(melanoma)	309740*
S2	TI,AB(melanomalignoma OR melanocarcinoma)	177°
S3	EMB.EXACT("metastatic melanoma")	15809*
S4	EMB.EXACT(melanoma)	162571*
S5	MESH.EXACT(melanoma)	91236*
S6	S1 OR S2 OR sS3 OR S4 OR S5	366099*
S7	MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year")	47333*
S8	TI,AB,IF(quality adjusted OR adjusted life year*)	162452*
S9	TI,AB,IF(qaly* OR qald* OR qale* OR qtime*)	37980*
S10	TI,AB,IF(illness state[*1] OR health state[*1])	1492893*
S11	TI,AB,IF(hui OR hui1 OR hui2 OR hui3)	7673*
S12	TI,AB,IF(multiattribute* OR multi attribute*)	18481*
S13	TI,AB,IF(utility NEAR/3 (score[*1] OR valu* or health* OR cost* OR measur* OR disease* OR mean OR gain or gains OR index*))	81075*
S14	TI,AB,IF(utilities)	683813*
S15	TI,AB,IF(eq-5d OR eq5d OR eq-5 OR eq5 OR euro qual OR euroqual OR euro qual5d OR euroqual5d OR euro qol OR euroqol OR euro qol5d OR euroqol5d OR euro quol OR euroquol OR euro quol5d OR euroquol5d OR eur qol OR eurqol OR eur qol5d OR eur qol5d OR eur?qul OR eur?qul5d OR euro* quality of life OR european qol)	82921*
S16	TI,AB,IF(euro* NEAR/3 (5*d OR 5d OR 5*dimension* OR 5dimension* OR 5*domain* OR 5domain*))	10812*
S17	TI,AB(sf6 OR sf 6 OR sf6d OR sf 6d OR sf six OR sfsix OR sf8 OR sf 8 OR sf eight OR sfeight)	85461*
S18	TI,AB(sf12 OR sf 12 OR sf twelve OR sftwelve)	45740*
S19	TI,AB(15D OR 15-D OR 15 dimension)	55759*

S20	TI,AB(sf16 OR sf 16 OR sf sixteen OR sfsixteen)	16842*
S21	TI,AB(sf20 OR sf 20 OR sf twenty OR sftwenty)	25576*
S22	TI,AB,IF(sf36* OR sf 36* OR sf thirtysix OR sf thirty six)	78108*
S23	TI,AB(standard gamble* OR sg)	32823*
S24	TI,AB,IF(time trade off[*1] OR time tradeoff[*1] OR tto OR timetradeoff[*1])	28942*
S25	TI,AB(rating scal*)	305435*
S26	TI,AB(linear scal*)	123446*
S27	TI,AB(linear analog*)	28369*
S28	TI,AB(visual analog* OR "VAS")	246904*
S29	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR (score[*1] or measure[*1]))	616839*
S30	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status) OR TI,AB,IF(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis"))	92135*
S31	EMB.EXACT("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30") OR TI,AB(EORTC QLQ-C30) OR TI,AB (EORTC*) OR EMB.EXACT("European Quality of Life 5 Dimensions questionnaire") OR EMB.EXACT("Short Form 36") OR EMB.EXACT("Functional Assessment of Cancer Therapy General") OR EMB.EXACT("Functional Assessment of Cancer Therapy G") OR TI,AB (Functional Assessment of Cancer Therapy) OR TI,AB(FACIT*)	57528*
S32	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	3627627*
S33	S6 AND S32	11646*
S34	TI,AB(case NEAR/1 (stud* OR report))	2136049*
S35	EMB.EXACT("Case study")	139388*
S36	EMB.EXACT("Abstract report" OR "Letter")	1226799*
S37	RTYPE("Case reports")	2240455*
S38	RTYPE("Letter")	2400935*
S39	RTYPE("Historical article")	367229*
S40	PSTYPE("Conference proceedings") AND PD(<20190101)	4327°
S41	(DTYPE("Conference review") OR DTYPE("Conference abstract") OR DTYPE("Conference Paper") OR	4166448*

	RTYPE("Conference abstract")) AND PD(<20190101)	
S42	RTYPE("Editorial")	1354263*
S43	RTYPE("Note")	881573*
S44	S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	12796542*
S45	S33 NOT S44	8869*
S46	S45 AND LA(english)	8581*
S47	advanced OR unresect* OR malign* OR metastat*	4132646*
S48	S46 AND S47	2348°
* Duplicates are removed from the search, but included in the result count. ° Duplicates are removed from the search and from the result count.		

Table 41: HRQoL Search Strategy for Embase, Medline, PsycInfo, and Econlit in ProQuest (11 November 2022)

Set#	Searched for	Results
S1	TI,AB(melanoma)	323774*
S2	TI,AB(melanomalignoma OR melanocarcinoma)	177°
S3	EMB.EXACT("metastatic melanoma")	16948*
S4	EMB.EXACT(melanoma)	170666*
S5	MESH.EXACT(melanoma)	95005*
S6	S1 OR S2 OR S3 OR S4 OR S5	383193*
S7	MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year")	50463*
S8	TI,AB,IF(quality adjusted OR adjusted life year*)	176564*
S9	TI,AB,IF(qaly* OR qald* OR qale* OR qtime*)	40826*
S10	TI,AB,IF(illness state[*1] OR health state[*1])	1550811*
S11	TI,AB,IF(hui OR hui1 OR hui2 OR hui3)	8121*
S12	TI,AB,IF(multiattribute* OR multi attribute*)	20381*
S13	TI,AB,IF(utility NEAR/3 (score[*1] OR valu* or health* OR cost* OR measur* OR disease* OR mean OR gain or gains OR index*))	86271*
S14	TI,AB,IF(utilities)	726395*
S15	TI,AB,IF(eq-5d OR eq5d OR eq-5 OR eq5 OR euro qual OR euroqual OR euro qual5d OR euroqual5d OR euro qol OR euroqol OR euro qol5d OR euroqol5d OR euro quol OR euroquol OR euro quol5d OR euroquol5d OR eur qol OR eurqol OR eur qol5d OR eur qol5d OR eur?qul OR eur?qul5d OR euro* quality of life OR european qol)	90040*
S16	TI,AB,IF(euro* NEAR/3 (5*d OR 5d OR 5*dimension* OR 5dimension* OR 5*domain* OR 5domain*))	11634*

S17	TI,AB(sf6 OR sf 6 OR sf6d OR sf 6d OR sf six OR sfsix OR sf8 OR sf 8 OR sf eight OR sfeight)	90362*
S18	TI,AB(sf12 OR sf 12 OR sf twelve OR sftwelve)	48606*
S19	TI,AB(15D OR 15-D OR 15 dimension)	58824*
S20	TI,AB(sf16 OR sf 16 OR sf sixteen OR sfsixteen)	17945*
S21	TI,AB(sf20 OR sf 20 OR sf twenty OR sftwenty)	27074*
S22	TI,AB,IF(sf36* OR sf 36* OR sf thirtysix OR sf thirty six)	81935*
S23	TI,AB(standard gamble* OR sg)	35153*
S24	TI,AB,IF(time trade off[*1] OR time tradeoff[*1] OR tto OR timetradeoff[*1])	31126*
S25	TI,AB(rating scal*)	322159*
S26	TI,AB(linear scal*)	134552*
S27	TI,AB(linear analog*)	29746*
S28	TI,AB(visual analog* OR "VAS")	263345*
S29	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR (score[*1] or measure[*1]))	668363*
S30	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status) OR TI,AB,IF(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis"))	96593*
S31	EMB.EXACT("European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30") OR TI,AB(EORTC QLQ-C30) OR TI,AB (EORTC*) OR EMB.EXACT("European Quality of Life 5 Dimensions questionnaire") OR EMB.EXACT("Short Form 36") OR EMB.EXACT("Functional Assessment of Cancer Therapy General") OR EMB.EXACT("Functional Assessment of Cancer Therapy G") OR TI,AB (Functional Assessment of Cancer Therapy) OR TI,AB(FACIT*)	63346*
S32	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	3834571*
S33	S6 AND S32	12430*
S34	TI,AB(case NEAR/1 (stud* OR report))	2257561*
S35	EMB.EXACT("Case study")	145049*
S36	EMB.EXACT("Abstract report" OR "Letter")	1261956*
S37	RTYPE("Case reports")	2301425*
S38	RTYPE("Letter")	2473572*
S39	RTYPE("Historical article")	368858*
S40	PSTYPE("Conference proceedings") AND	4327°

	PD(<20190101)	
S41	(DTYPE("Conference review") OR DTYPE("Conference abstract") OR DTYPE("Conference Paper") OR RTYPE("Conference abstract")) AND PD(<20190101)	4176849*
S42	RTYPE("Editorial")	1415678*
S43	RTYPE("Note")	915855*
S44	S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	13127769*
S45	S33 NOT S44	9587*
S46	S45 AND LA(english)	9286*
S47	advanced OR unresect* OR malign* OR metastat*	4420974*
S48	S46 AND S47	3154°
S49	S48 AND PD(>20220123)	289°
* Duplicates are removed from the search, but included in the result count. ° Duplicates are removed from the search and from the result count.		

Economic modelling

C11. Priority question: Resource use estimates following treatment initiation (CS, Table 50) are reported to be from TA400. However, the resource use estimates in Table 50 are higher than those reported in TA400. Please explain this inconsistency.

The resource use estimates and percentage of patients assumed to be receiving each resource use item in the cost-effectiveness model are the same as those reported in TA400 for the treatment initiation period (as reported in CS Document B Table 51). The overall cost of healthcare resource use in the treatment initiation period is higher in the cost-effectiveness model because the unit costs used to generate an overall cost are taken from the latest available NHS reference costs (2020/2021) which are higher than those used in TA400.

The percentage of patients requiring each resource in a cycle used in the cost-effectiveness model is consistent with those reported in TA400.

The resource use estimates used to calculate per-cycle healthcare resource use costs (CS Document B Table 50) are incorrect. We thank the EAG for pointing out this error in the company submission. Corrected resource use estimates per cycle are presented in Table 42. Please note, the correct resource use estimates were presented to clinicians at an advisory board, and that this mistake was merely an error in model development.

The resulting estimates of cost per cycle in each year after treatment are presented in Table 43. As these estimates are used to calculate costs for all model arms, there is a large impact on incremental costs for nivolumab-relatlimab versus comparators. Table 44 presents the impact on total HCRU costs when using the corrected resource use estimates.

It is important to note that this correction to ‘per cycle resource use’ in turn impacts base case analyses and sensitivity analyses. Base case deterministic results (full incremental analysis) with this correction applied are presented in Table 45. An updated model and full results will be provided prior to technical engagement.

Table 42: Healthcare resource use per cycle

Resource use item	Resource use per cycle		
	Year 1	Year 2	Year 3
Medical oncologist consultation	1.9	1.9	1.9
Radiation oncologist consultation	1	1.0	1.0
GP consultation	2	2.0	2.0
Brain MRI	0.3	0.3	0.3
PET-CT scan	0.4	0.4	0.4
Nurse visit	1	1.0	1.0
Oncology general ward - inpatient	1.3	1.3	1.3
Complete blood count	1.3	1.3	1.3
Complete metabolic panel	1.3	1.3	1.3
Lactate dehydrogenase	1.3	1.3	1.3
CT scan (any)	1	1.0	1.0
Bone scintigraphy	0.3	0.3	0.3
Echography	0.3	0.1	0.1
Chest x-ray	1.1	1.1	1.1
Plastic surgeon consultation	1.5	1.5	1.5
Key: CT, computerised tomography; GP, general practitioner; MRI, magnetic resonance imaging; PET, positron emission tomography.			

Table 43: Healthcare resource use costs per cycle

Year after entering the model	Per-cycle cost
Year 1	£658.80
Year 2	£328.60
Year 3+	£197.40

Table 44: Impact on total costs of the correction to resource use estimates

Treatment	Total HCRU costs, uncorrected (CS Appendix J Tables 37-39)	Total HCRU costs, corrected
Nivolumab-relatlimab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]

Pembrolizumab	[redacted]	[redacted]

Table 45: Base-case results – with PAS for all BMS assets, pembrolizumab at list price (corrected)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,426
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.

Palliative care costs are applied differently in the cost-effectiveness model than in TA400. In the cost-effectiveness model, for simplicity, they are applied as a one-off cost in the third cycle before death, however in TA400 these costs are applied over the 12 weeks preceding death. To account for this, palliative care resource use estimates used in the model are three times higher than those reported in TA400.

C12. Priority question: Please clarify whether resource use estimates associated with treatment initiation (CS, Table 51) are included in the Year 1 resource use estimates.

Treatment initiation costs are not included in the Year 1 resource use estimates but applied as a separate one-off cost in the first model cycle. In the results summaries, these costs are included in the sum of costs in the progression-free health state (CS Document B Appendix J, Table 34-36 and Table 40-42).

C13. Please explain the rationale for applying a one-off end of life care cost in addition to a one-off palliative care cost, in the cycle prior to death.

The application of an end-of-life cost and separate palliative care cost follows the approach used in TA400. Additionally, the palliative care cost is applied in the third cycle before death to reflect the period of time in which a patient would receive palliative care. The end-of-life cost used reflects a hospice stay for the patient rather than treatment received.

C14. In the company model, the time-varying NMA HRs (OS and PFS) were applied to the selected nivolumab curve to generate nivolumab+ipilimumab and pembrolizumab survival estimates. When a constant HR was applied, the nivolumab+relatlimab extrapolation was used as the reference treatment.

Please explain why the reference treatment differed depending on whether time-varying or constant HRs were applied. In addition, please provide constant OS and PFS HRs for nivolumab+ipilimumab versus nivolumab and for pembrolizumab versus nivolumab.

The use of a differing reference treatment was an oversight, we thank the EAG for bringing this to our attention. The requested constant HRs for OS and PFS are provided in Table below. As noted in CS Document B Section B.3.3.3.2. as the proportional hazards assumption did not hold for all the studies in the NMA, fractional polynomial NMAs (which provide time-varying treatment effects) were used in the analyses of nivolumab + ipilimumab and pembrolizumab, not constant HRs.

Table 46: NMA results - constant hazard ratios

	PFS constant HR (95% CI)	OS constant HR (95% CI)
Nivolumab + ipilimumab vs. nivolumab	[redacted]	[redacted]
Pembrolizumab vs. nivolumab	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio.

C15. In the company model, the maximum timepoint (in months) at which time-varying HRs are applied for nivolumab+ipilimumab is 98 for OS (cell reference: OS!DE84) and 96 for PFS (cell reference: PFS!EX127). These timepoints are inconsistent with the values in the OS Data sheet (cell reference: OS Data!J132) and PFS Data sheet (cell reference: PFS Data!J162).

Please clarify which maximum follow-up timepoints are correct.

We can confirm that the value of [redacted] months for OS and [redacted] months for PFS are the correct values to denote the maximum timepoint (in months).

References

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2. Zettler ME, Lee CH, Gajra A and Feinberg BA. Assessment of objective response rate (ORR) by investigator versus blinded independent central review in pivotal trials of drugs approved for solid tumor indications. *Journal of Clinical Oncology*. 2021; 39(15_suppl):e13570-e.
3. (EMA) EMA. Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man: Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. 2012.
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7. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997; 35(11):1095-108.
8. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *The Lancet Oncology*. 2019; 20(9):1239-51.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Results addendum

(updated results in response to EAG clarification questions)

May 2023

Contents

Tables and figures

1. Updated results of the cost-effectiveness analysis

1.1. Updated results section of Document B

This section presents the results of the cost-effectiveness analysis presented in Section B.3.9 and B.3.10 of Document B incorporating the health care resource use estimates amended following EAG clarification questions.

1.1.1. Base case results

1.1.1.1. Probabilistic analysis

Probabilistic sensitivity analysis (PSA) was performed to account for joint uncertainties in the key model inputs, in which multiple input parameters were varied simultaneously by sampling their values from uncertainty distributions for 1,000 iterations. Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on parameter variability, a standard error of 10% of the mean was assumed.

1.1.1.1.1. Probabilistic sensitivity analysis results at list prices

The results of the PSA are presented in Table 1 to Table 4. The cost-effectiveness plane is presented in Figure 1. This plots the mean incremental costs and QALYs (relative to nivolumab-relatlimab) from the PSA alongside the deterministic incremental costs and QALYs to highlight the effect of parameter uncertainty on the model results.

Table 1: Mean PSA results, full incremental analysis - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	Incr. ICER
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated

Nivolumab + ipilimumab	[redacted]						£52,905
Nivolumab-relatlimab	[redacted]						£115,076
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.							

Table 2: Mean PSA pairwise results nivolumab-relatlimab versus nivolumab - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]						
Nivolumab-relatlimab	[redacted]						£76,681
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 3: Mean PSA pairwise results - nivolumab-relatlimab versus nivolumab + ipilimumab - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]						
Nivolumab-relatlimab	[redacted]						£115,076
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 4: Mean PSA pairwise results - nivolumab-relatlimab versus pembrolizumab - list prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Pembrolizumab	[redacted]						
Nivolumab-relatlimab	[redacted]						£34,961
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA with list prices is shown in Figure 1. The willingness-to-pay threshold presented in this figure represents a willingness-to-pay threshold of £30,000 per QALY gained.

Figure 1: Cost effectiveness plane relative to nivolumab-relatlimab - list prices

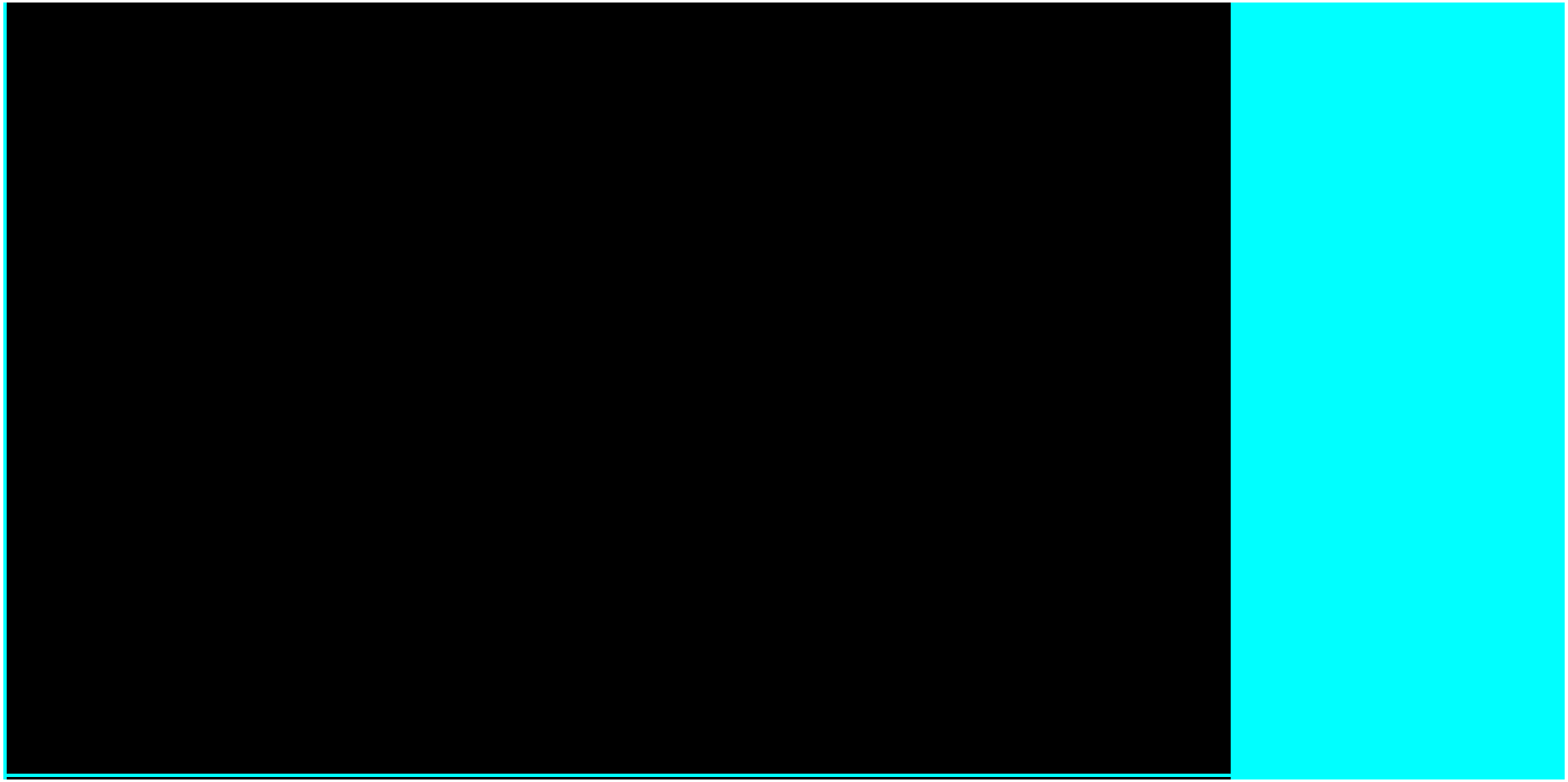


Figure 2 presents the cost-effectiveness acceptability curve, showing the likelihood of each comparator being the most cost-effective at different willingness-to-pay thresholds.

Figure 2: Cost-effectiveness acceptability curve (CEAC) - list prices

1.1.1.1.2. Probabilistic sensitivity analysis results incorporating confidential discounts

Results of the probabilistic sensitivity analysis incorporating confidential discounts for nivolumab, nivolumab-relatlimab, and nivolumab + ipilimumab are presented in Table 5 to Table 8 (the magnitude of discount for pembrolizumab is unknown so not included).

Table 5: Mean PSA results, full incremental analysis – PAS prices for all BMS assets, pembrolizumab at list price

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	Incr. ICER
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,107
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality adjusted life year.							

Table 6: Mean PSA pairwise results nivolumab-relatlimab versus nivolumab – PAS prices for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]	[redacted]	[redacted]	–	–	–	–
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,107
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 7: Mean PSA pairwise results - nivolumab-relatlimab versus nivolumab + ipilimumab – PAS prices for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	–	–	–	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 8: Mean PSA pairwise results - nivolumab-relatlimab versus pembrolizumab – PAS prices for all BMS assets, pembrolizumab at list price

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Pembrolizumab	[redacted]	[redacted]	[redacted]	–	–	–	
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA with PAS prices incorporated for all BMS assets is shown in Figure 3. The willingness-to-pay threshold presented in this figure represents a threshold of £30,000 per QALY gained.

Figure 3: Cost-effectiveness plane incorporating confidential discounts for all BMS assets, pembrolizumab at list price

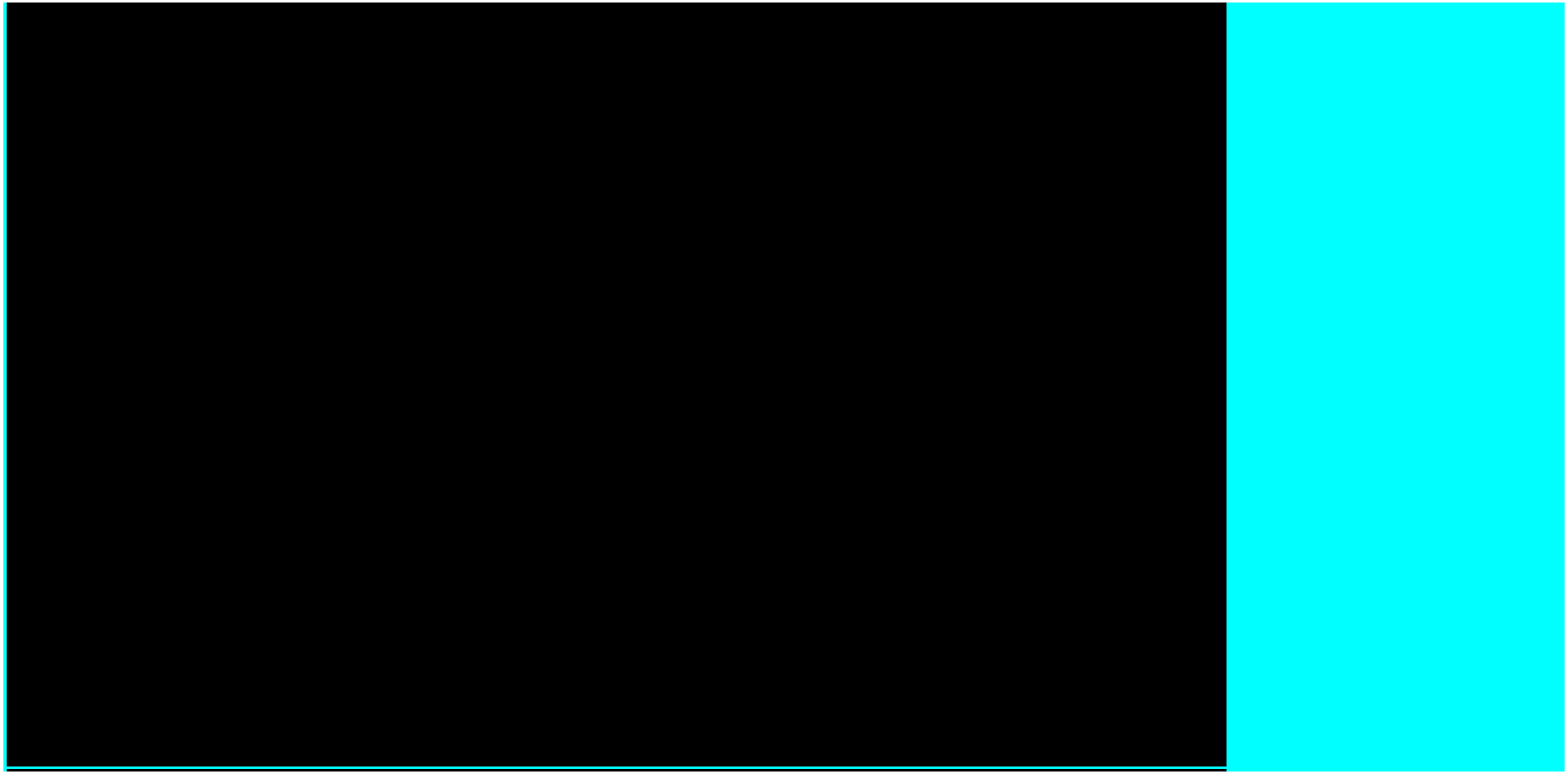
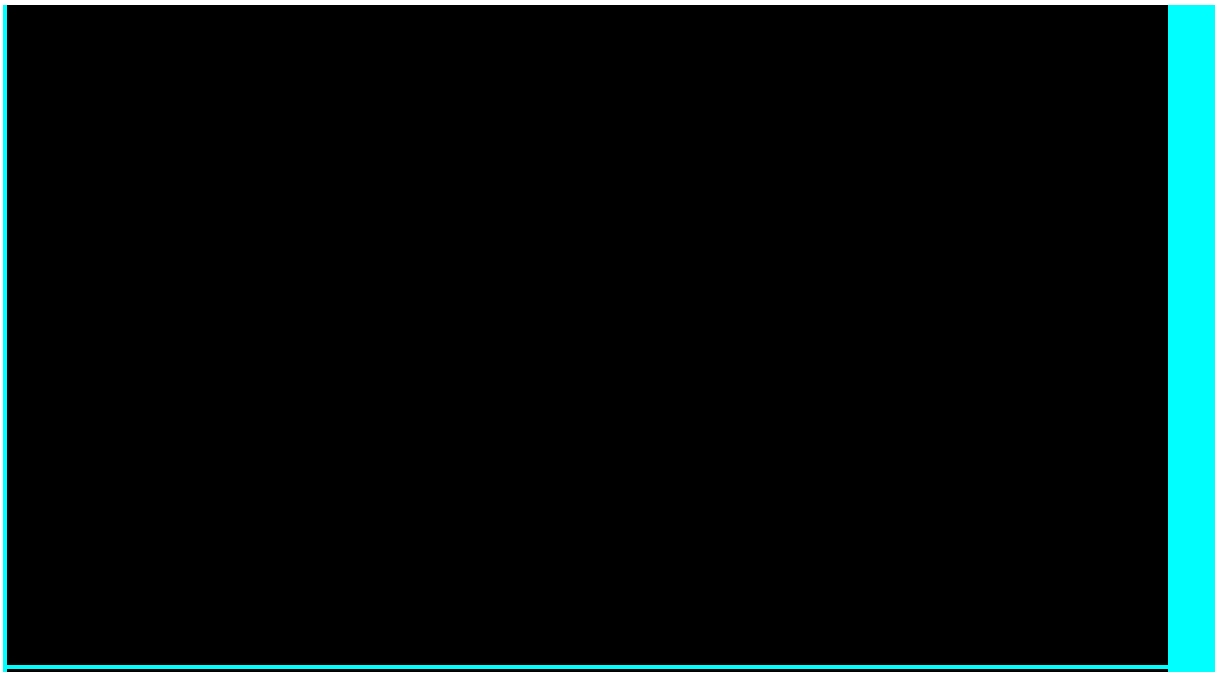


Figure 4 presents cost-effectiveness acceptability curves for each model arm, showing the likelihood of each comparator being the most cost-effective at different willingness-to-pay thresholds when confidential discounts for all BMS assets are incorporated.

Figure 4: Cost-effectiveness acceptability curves (CEAC) - PAS prices for all BMS assets, pembrolizumab at list price



1.1.1.2. Base case deterministic incremental cost-effectiveness analysis results

1.1.1.2.1. Base case deterministic results at list prices

Fully incremental base case results at list prices are presented in Table 9. Disaggregated results are available in Appendix J. Results of the pairwise analysis against all comparators are presented in Table 10 to Table 12.

Table 9: Base-case results – List prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,646
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£125,634
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years.							

Table 10: Base-case pairwise results nivolumab-relatlimab versus nivolumab monotherapy – List prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£81,898
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 11: Base-case pairwise results – nivolumab-relatlimab versus nivolumab + ipilimumab – List prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£125,634
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 12: Base-case pairwise results – nivolumab-relatlimab versus pembrolizumab – List prices

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Pembrolizumab	[redacted]	[redacted]	[redacted]	– -	– -	– -	-

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,509
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

1.1.1.2.2. Base case deterministic results incorporating confidential discounts

The full incremental cost-effectiveness results with prices incorporating confidential discounts for all BMS assets are presented in Table 13. Pairwise analyses are presented with confidential discounts included for all BMS assets in Table 14 to Table 16.

Table 13: Base-case results – with PAS for all BMS assets, pembrolizumab at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER incremental (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,426
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Strictly Dominated
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 14: Base-case pairwise results nivolumab-relatlimab versus nivolumab monotherapy – with PAS for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,426
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 15: Base-case pairwise results - nivolumab-relatlimab versus nivolumab + ipilimumab – with PAS for all BMS assets

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 16: Base-case pairwise results - nivolumab-relatlimab versus pembrolizumab – with PAS for all BMS assets, pembrolizumab at list price

Treatment	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Nivolumab-relatlimab dominates
Key: LY, life year; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

1.1.2. Exploring uncertainty

1.1.2.1. Deterministic sensitivity analysis

For one-way sensitivity analysis (OWSA), values for all parameters with univariate uncertainty distributions were set to their upper and lower limits reported in Appendix O.

1.1.2.1.1. Deterministic sensitivity analysis results at list prices

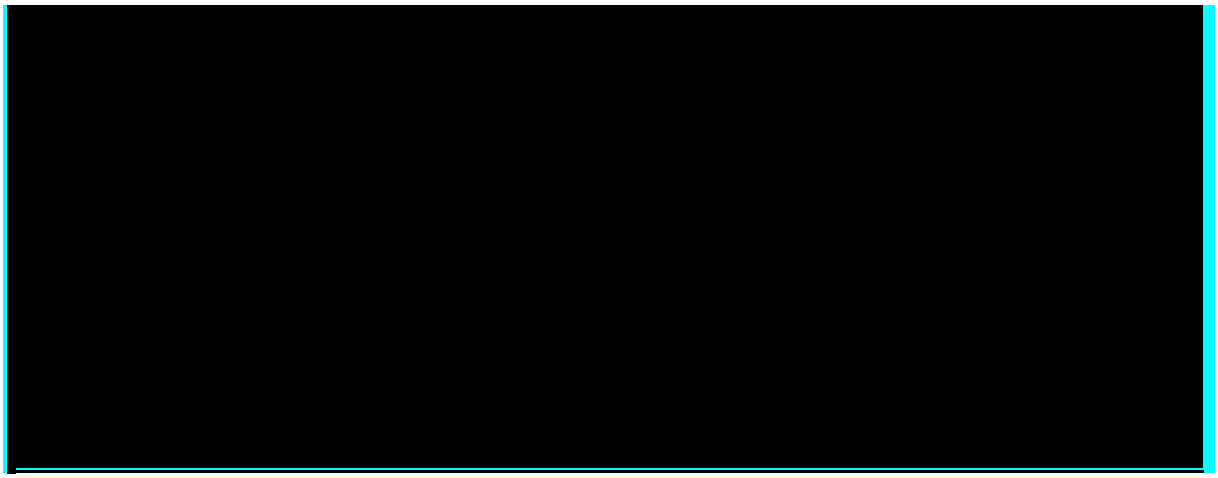
Figure 5 to Figure 7 present the results of the OWSA in the form of tornado diagrams. Each figure shows the 10 parameters with the most influence on the ICER for each pairwise comparison with nivolumab-relatlimab. Health state utilities and inputs used to calculate the cost of health care resource use in the model are among the most influential for each comparator. For the comparison against nivolumab +

ipilimumab, the incidence and cost of treating colitis are in the 10 most influential parameters, whilst no AE inputs feature in the most influential parameters for the ICER against nivolumab or pembrolizumab. This reflects the relative safety profile of nivolumab + ipilimumab compared to other modelled regimens.

Figure 5: Deterministic sensitivity analysis tornado diagram, versus nivolumab – list prices

Figure 6: Deterministic sensitivity analysis tornado diagram, versus nivolumab + ipilimumab – list prices

Figure 7: Deterministic sensitivity analysis tornado diagram, versus pembrolizumab – list prices



1.1.2.1.2. Deterministic sensitivity analysis results incorporating confidential discounts

The results of the OWSA with PAS discounts incorporated for all BMS assets are presented in Figure 8 to Figure 10 as tornado diagrams showing the 10 parameters with the most influence on the ICER against each comparator. In each comparison health state utility values, and the inputs used to calculated the cost of health care resource use are among the most influential parameters. As with the list price OWSA, in the comparison against nivolumab + ipilimumab, the cost and incidence of colitis are amongst the most influential parameters.

Figure 8: Deterministic sensitivity analysis tornado diagram, versus nivolumab – PAS prices

Figure 9: Deterministic sensitivity analysis tornado diagram, versus nivolumab + ipilimumab – PAS prices for all BMS assets

Figure 10: Deterministic sensitivity analysis tornado diagram, versus pembrolizumab – PAS prices for all BMS assets, pembrolizumab at list price

1.1.2.2. Scenario analysis

To test the sensitivity of the model to changing one or more model inputs or structural assumptions, a number of scenarios were tested.

1.1.2.2.1. Scenario analysis results – list prices

Table 17 describes the scenarios tested and presents the impact on the ICER with all modelled treatments at list price. The most impactful scenarios across all comparisons are the application of stopping rules for all treatment arms at 5 years rather than 2 years in the base case; the choice of model used to extrapolate nivolumab-relatlimab; the source of health state utility values; and not capping TTD by PFS. Figure 11 to Figure 13 graphically show the most influential scenarios on the ICER for each pairwise comparator.

Figure 11: Scenario analysis tornado diagram versus nivolumab - list prices

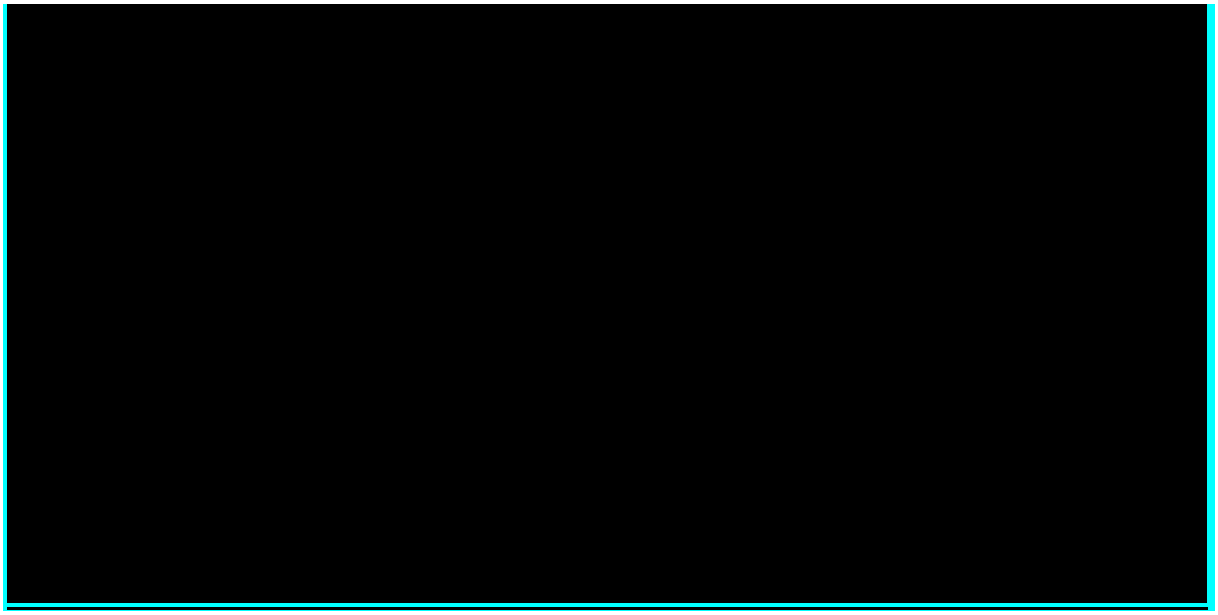


Figure 12: Scenario analysis tornado diagram versus nivolumab + ipilimumab - list prices

Figure 13: Scenario analysis tornado diagram versus pembrolizumab - list prices

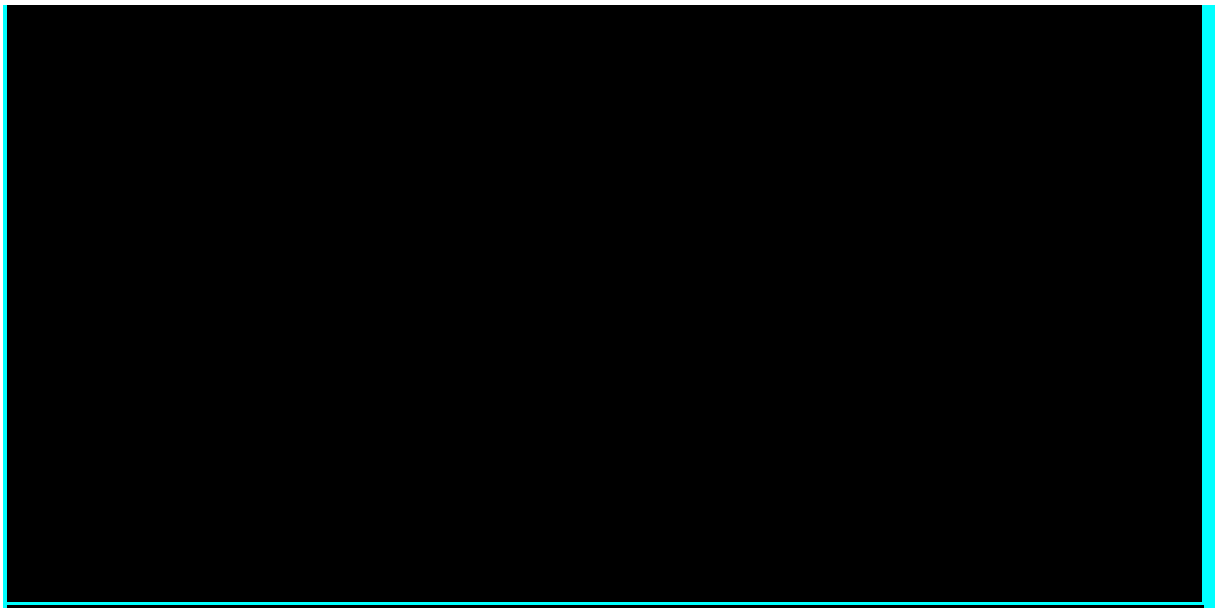


Table 17: Scenario analysis – List prices

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
	Base case		£81,898	£125,634	£33,509
1	1.5% discounting		[redacted]	[redacted]	[redacted]
2	NICE Melanoma HEMR health state utilities	Alternative source of utilities. (Section B.3.4.5)	[redacted]	[redacted]	[redacted]
3	No-age adjustment to utilities	Explore the impact of age-related utility adjustment. (Section B.3.4.5)	[redacted]	[redacted]	[redacted]
4	Stopping rules applied at 5 years	Available evidence suggests some treatment occurs beyond official stopping rules. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
5	10% of patients continue/reinitiate IO treatment after 2 years	UK clinical validation (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
6	Pembrolizumab TTE equal to nivolumab	UK clinical validation (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
7	Nivolumab-relatlimab and nivolumab OS generalized gamma	Lack of long-term data for nivolumab-relatlimab survival outcomes. Settings also applied to nivolumab for consistency. Next most	[redacted]	[redacted]	[redacted]
8	Nivolumab-relatlimab and nivolumab PFS 1 knot odds spline model		[redacted]	[redacted]	[redacted]

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
		plausible extrapolating model. (Section B.3.3.2)			
9	Time horizon 30 years		[redacted]	[redacted]	[redacted]
10	TTD not capped by PFS	To explore potential treatment beyond progression. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
11	Nivolumab-relatlimab TTD gamma model	Lack of long-term data for nivolumab-relatlimab TTD. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
12	Nivolumab CheckMate-067 KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
13	Pembrolizumab SACT KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)	[redacted]	[redacted]	[redacted]
14	Nivolumab-relatlimab subsequent treatment proportion equal to nivolumab	Alternative assumption on subsequent treatment proportion (Section B.3.5.4.1)	[redacted]	[redacted]	[redacted]
15	Reduction in subsequent treatment proportions by 20% (all treatment arms)	Alternative assumption on subsequent treatment proportions (Section B.3.5.4.1)	[redacted]	[redacted]	[redacted]

Key: HEMR, health economic modelling report; IO, immune-oncology; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy database; TTD, time to treatment discontinuation; TTE, time to event.

1.1.2.2.2. Scenario analysis results – incorporating confidential discounts

Table **18** describes the scenarios tested and presents the impact on the ICER with confidential discounts incorporated for all BMS assets. In the comparisons with nivolumab and nivolumab + ipilimumab the most influential scenarios are the application of a stopping rule for all model arms at 5 years rather than 2 years; the choice of nivolumab-relatlimab TTE extrapolations; and setting discount rates to 1.5%. The most impactful scenarios in the comparison to pembrolizumab are the variation of confidential discounts applied to pembrolizumab. Figure 14 to Figure 16 graphically show the most influential scenarios on the ICER for each pairwise comparator.

Figure 14: Scenario analysis tornado diagram versus nivolumab – PAS prices for all BMS assets

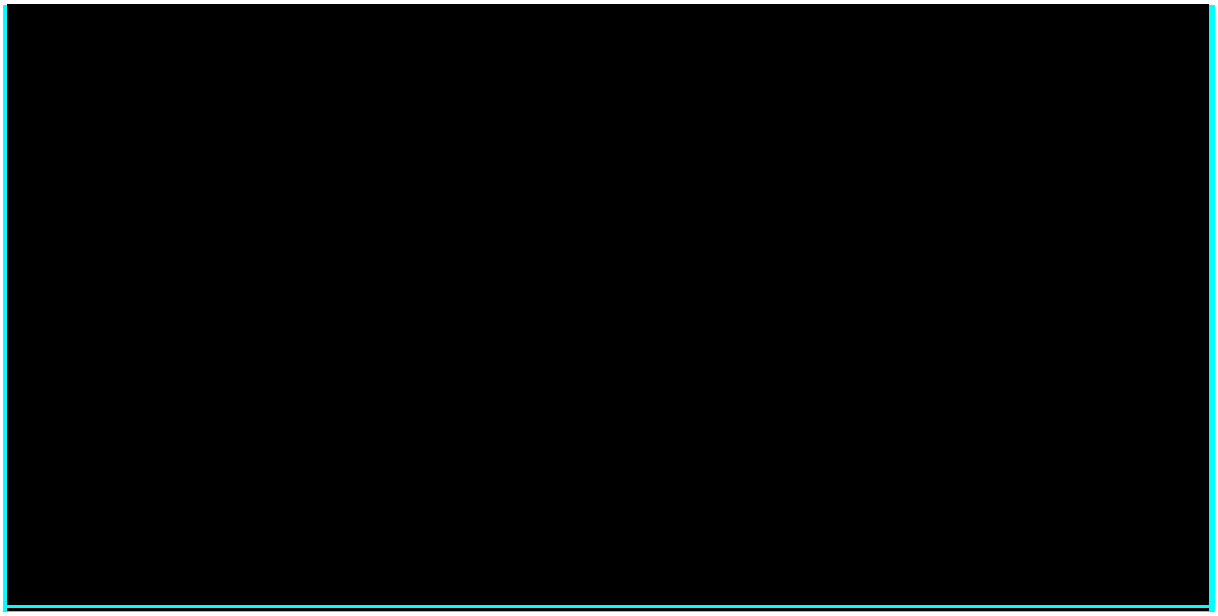


Figure 15: Scenario analysis tornado diagram versus nivolumab + ipilimumab – PAS prices for all BMS assets

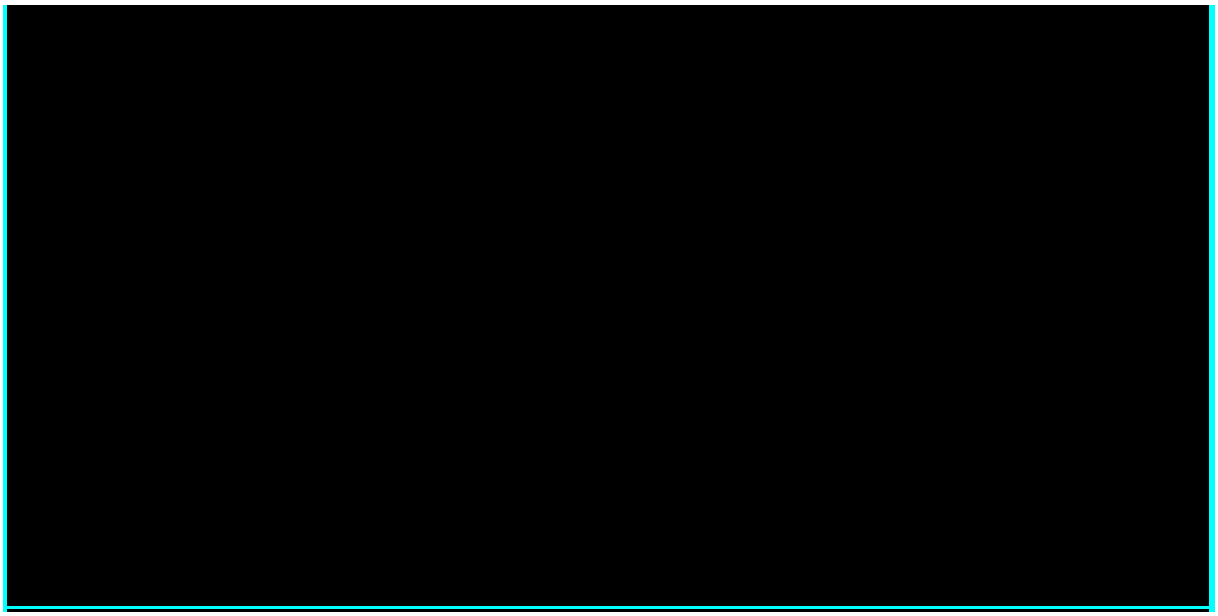


Figure 16: Scenario analysis tornado diagram versus pembrolizumab – PAS prices for all BMS assets, pembrolizumab at list price

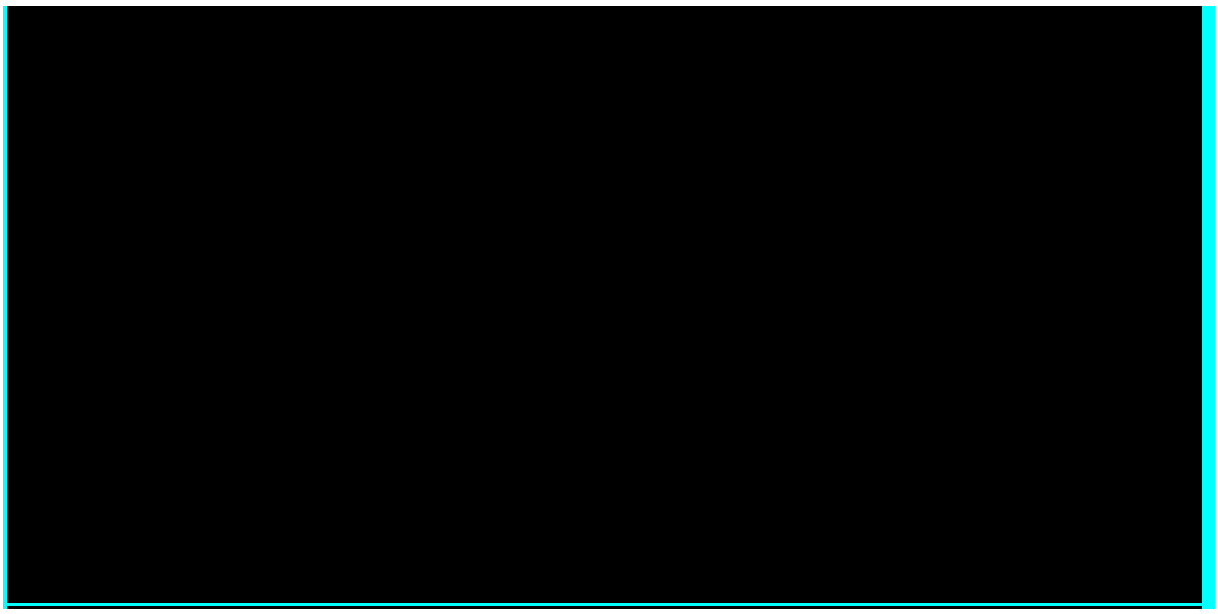


Table 18: Scenario analysis – incorporating confidential discounts for all BMS assets, pembrolizumab at list price

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
	Base case		£20,426	Nivolumab-relatlimab dominates	Nivolumab-relatlimab dominates
1	1.5% discounting				
2	NICE Melanoma HEMR health state utilities	Alternative source of utilities. (Section B.3.4.5)			
3	No-age adjustment to utilities	Explore the impact of age-related utility adjustment. (Section B.3.4.5)			
4	Stopping rules applied at 5 years	Available evidence suggests some treatment occurs beyond official stopping rules. (Section B.3.3.2)			
5	10% of patients continue/reinitiate IO treatment after 2 years	UK clinical validation (Section B.3.3.2)			
6	Pembrolizumab TTE equal to nivolumab	UK clinical validation (Section B.3.3.2)			
7	Nivolumab-relatlimab and nivolumab OS generalized gamma	Lack of long-term data for nivolumab-relatlimab survival outcomes. Settings also applied to nivolumab for consistency. Next most plausible extrapolating model. (Section B.3.3.2)			
8	Nivolumab-relatlimab and nivolumab PFS 1 knot odds spline model				
9	Time horizon 30 years				

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
10	TTD not capped by PFS	To explore potential treatment beyond progression. (Section B.3.3.2)			
11	Nivolumab-relatlimab standard gamma model (TTD)	Lack of long-term data for nivolumab-relatlimab TTD. (Section B.3.3.2)			
12	Nivolumab CheckMate-067 KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)			
13	Pembrolizumab SACT KM data (TTD)	Alternative source of TTD data. (Section B.3.3.2)			
14	Nivolumab-relatlimab subsequent treatment proportion equal to nivolumab	Alternative assumption on subsequent treatment proportion (Section B.3.5.4.1)			
15	Reduction in subsequent treatment proportions by 20% (all treatment arms)	Alternative assumption on subsequent treatment proportions (Section B.3.5.4.1)			
16	Pembrolizumab discount set to 0%	The discount applied to pembrolizumab is unknown			
17	Pembrolizumab discount set to 45%				
18	Pembrolizumab discount set to 50%				
19	Pembrolizumab discount set to 55%				
20	Pembrolizumab discount set to 60%				

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
21	Pembrolizumab discount set to 65%				
22	Pembrolizumab discount set to 70%				
23	Pembrolizumab discount set to 75%				
24	Pembrolizumab discount set to 80%				
25	Pembrolizumab discount set to 85%				
26	Pembrolizumab discount set to 90%				
27	Pembrolizumab discount set to 100%				
28	Pembrolizumab discount set to 95%				
29	Pembrolizumab discount set to 5%				
30	Pembrolizumab discount set to 10%				
31	Pembrolizumab discount set to 15%				
32	Pembrolizumab discount set to 20%				
33	Pembrolizumab discount set to 25%				

	Parameter	Justification	ICER versus nivolumab	ICER versus nivolumab + ipilimumab	ICER versus pembrolizumab
34	Pembrolizumab discount set to 30%		[redacted]	[redacted]	[redacted]
35	Pembrolizumab discount set to 35%		[redacted]	[redacted]	[redacted]
36	Pembrolizumab discount set to 40%		[redacted]	[redacted]	[redacted]

Key: HEMR, health economic modelling report; IO, immune-oncology; KM, Kaplan Meier; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy database; TTD, time to treatment discontinuation; TTE, time to event.

1.2. Updates to Appendix J.2

This section presents the disaggregated results of the cost-effectiveness analysis presented in Appendix J.2 incorporating the health care resource use estimates amended following EAG clarification questions.

Summaries of costs for each comparator according to health state and cost category at list price are presented in Table 19 to Table 21 and Table 22 to Table 24 respectively. The same results are presented with the incorporation of confidential discounts for nivolumab-relatlimab and all comparators in Table 25 to Table 27, and Table 28 to Table 30 respectively.

Table 19: Summary of costs by health state versus nivolumab (List price)

Health state	Nivolumab-relatlimab - Costs	Nivolumab - Costs	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (end-of-life)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Summary of costs by health state versus nivolumab + ipilimumab (list price)

Health state	Nivolumab-relatlimab - Costs	Nivolumab + ipilimumab - Costs	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (end-of-life)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 21: Summary of costs by health state versus pembrolizumab (list price)

Health state	Nivolumab-relatlimab - Costs	Pembrolizumab - Costs	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (end-of-life)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22: Summary of predicted resource use by category of cost versus nivolumab (list prices)

Cost group	Nivolumab-relatlimab - Costs	Nivolumab - Costs	Increment	Absolute increment	% absolute increment
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource-use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 23: Summary of predicted resource use by category of cost versus nivolumab + ipilimumab (list prices)

Cost group	Nivolumab-relatlimab - Costs	Nivolumab + ipilimumab - Costs	Increment	Absolute increment	% absolute increment
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent treatment costs					
Subsequent administration costs					
Adverse event costs					
Resource-use costs					
Total					

Table 24: Summary of predicted resource use by category of cost versus pembrolizumab (list prices)

Cost group	Nivolumab-relatlimab - Costs	Pembrolizumab - Costs	Increment	Absolute increment	% absolute increment
Treatment costs					
Administration costs					
Subsequent treatment costs					
Subsequent administration costs					
Adverse event costs					
Resource-use costs					
Total					

Table 25: Summary of costs by health state versus nivolumab (PAS prices for BMS assets)

Health state	Nivolumab-relatlimab - Costs	Nivolumab - Costs	Increment	Absolute increment	% absolute increment
Progression-free					
Progressed					
Death (end-of-life)					
Total					

Table 26: Summary of costs by health state versus nivolumab + ipilimumab (PAS prices for BMS assets)

Health state	Nivolumab-relatlimab - Costs	Nivolumab + ipilimumab - Costs	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (end-of-life)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 27: Summary of costs by health state versus pembrolizumab (PAS prices for BMS assets, pembrolizumab at list price)

Health state	Nivolumab-relatlimab - Costs	Pembrolizumab - Costs	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (end-of-life)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28: Summary of predicted resource use by category of cost versus nivolumab (PAS prices for BMS assets)

Cost group	Nivolumab-relatlimab - Costs	Nivolumab - Costs	Increment	Absolute increment	% absolute increment
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource-use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 29: Summary of predicted resource use by category of cost versus nivolumab + ipilimumab (PAS prices for BMS assets)

Cost group	Nivolumab-relatlimab - Costs	Nivolumab + ipilimumab - Costs	Increment	Absolute increment	% absolute increment
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource-use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30: Summary of predicted resource use by category of cost versus pembrolizumab (PAS prices for BMS assets, pembrolizumab at list price)

Cost group	Nivolumab-relatlimab - Costs	Pembrolizumab - Costs	Increment	Absolute increment	% absolute increment
Treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource-use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	Dr Mark Harries
2. Name of organisation	Melanoma Focus
3. Job title or position	Chairman of Melanoma Focus
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	**Melanoma Focus, a national UK charity is unique in its field, combining the functions of patient support and advocacy with the role of providing representation and up-to-date scientific information for UK healthcare professionals involved in melanoma. Melanoma Focus organises two professional meetings a year, creates guidelines on rare melanomas using NICE-accredited methodology and produces other consensus guidelines.** **Funding is from personal donations and fundraising activities, professional membership, sponsorship and grants for various activities**
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	**Melanoma Focus has received funding from BMS and other Pharma in the field of melanoma as sponsorship for meetings and activities.** Funding has always been multiple Pharma supporting meetings/projects

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve progression-free survival for patients with stage 4 and unresectable stage 3 melanoma.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A hazard ratio for progression of 0.8 or better compared to giving nivolumab alone
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Single agent PD-1 inhibitors (Nivolumab or Pembrolizumab) or combination PD-1 and CTLA-4 inhibition (ipilimumab and nivolumab). For patients with rapidly progressive life-threatening BRAF mutated melanoma treatment maybe with BRAF/MEK inhibition (dabrafenib/trametinib or encorafenib/binimetinib).
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline [NG14] Published: 29 July 2015 Last updated: 27 July 2022
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The choice of whether to use single agent PD-1 inhibitors (Nivolumab or Pembrolizumab) or combination PD-1 and CTLA-4 inhibition (ipilimumab and nivolumab) will vary according to the individual circumstances of the patient and oncologists' opinion.
9c. What impact would the technology have on the current pathway of care?	More patients could be offered combination treatment without the toxicity associated with ipilimumab and nivolumab
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If approved, then Nivolumab-relatlimab will replace ipilimumab and nivolumab for a proportion of patients
10a. How does healthcare resource use differ between the technology and current care?	Fewer side effects and hence easier management of toxicities would be expected if approved for use.
10b. In what clinical setting should the technology be used? (For example,	Will be delivered in specialist melanoma clinics/cancer units

primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil other than drug and pharmacy costs
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
11a. Do you expect the technology to increase length of life more than current care?	Yes compared to single agent nivolumab and on a par with ipilimumab and nivolumab
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients for whom the toxicities of ipilimumab and nivolumab would be difficult.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or	No more difficult

healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No –as long as the side effect profiles of the competitors is factored in.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the	Yes

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	yes
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – patients not suitable for ipilimumab and nivolumab
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Well documented immune-therapy related side effects

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	twice the median progression-free survival and a 25% lower risk of disease progression or death than nivolumab alone (hazard ratio, 0.75; P=0.006 by the log-rank test)
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	n/a
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	n/a
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	n/a

21. How do data on real-world experience compare with the trial data?	comparable

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	n/a
22b. Consider whether these issues are different from issues with current care and why.	n/a

Topic-specific questions

23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Nivolumab and Relatlimab improves progression free survival compared to Nivolumab alone • Nivolumab and Relatlimab has less toxicity than Nivolumab and ipilimumab. • The use of relatlimab will pose no additional challenges for melanoma healthcare professionals used to dealing with immunotherapy. •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our privacy notice.

EAG STA REPORT (V3)

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135967

Completed 17 July 2023

CONTAINS [redacted]
AND [redacted] DATA

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

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Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
Nigel Fleeman	Critical appraisal of the clinical evidence
Angela Stainthorpe	Critical appraisal of the economic model
Sam Bryning	Critical appraisal of the economic model
Sarah Nevitt	Critical appraisal of the statistical evidence
James Mahon	Critical appraisal of the economic model
Sophie Beale	Critical appraisal of the evidence, editorial input
Angela Boland	Critical appraisal of the evidence, editorial input
Yenal Dundar	Critical appraisal of the search strategies
Ashley Marsden	Critical appraisal of the company submission
Sarah Danson	Clinical advice and critical appraisal of the clinical evidence

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AE	adverse event
AIC	Akaike Information Criteria
AJCC	American Joint Committee on Cancer
BIC	Bayesian Information Criteria
BICR	blinded independent central review
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CrI	credible interval
CS	company submission
CSR	clinical study report
EAG	external assessment group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
FACIT GP5	Functional Assessment of Chronic Illness Therapy item GP5
FACT-G	Functional Assessment of Cancer Therapy-general
FACT-M	Functional Assessment of Cancer Therapy-melanoma
FDA	US Food and Drug Administration
FDC	fixed dose combination
FE	fixed-effects
FP	fractional polynomial
HEMR	health economic modelling report
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IMAE	immune-mediated adverse event
IO	immune-oncology
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
KM	Kaplan–Meier
LAG-3	lymphocyte-activation gene-3
MEK	mitogen-activated extracellular signal-regulated kinase
MHRA	UK Medicines and Healthcare products Regulatory Agency
MID	minimally important difference
MS	melanoma subscale
NG14	NICE melanoma assessment and management guidelines
NMA	network meta-analysis
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PD	progressed disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1

PF	progression free
PFS	progression-free survival
PFS2	progression-free survival after the next line of therapy
PH	proportional hazard
PLD	patient level data
PRO	patient reported outcome
PS	performance status
PSS	Personal Social Services
Q4W	every 4 weeks
QALY	quality adjusted life years
RCT	randomised controlled trial
SAE	serious adverse event
SLR	systematic literature review
SmPC	Summary of Product Characteristics
TA	technology appraisal
TRAE	treatment-related adverse event
TTD	time to treatment discontinuation

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Section 1.6 outlines the key cost effectiveness issues identified by the EAG.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table A Summary of key issues

Issue	Summary of issue	Report sections
Issue 1	Lack of clinical trial evidence for patients aged 12 to 18 years	2.2.3, 2.3.2, 3.1 and 3.8
Issue 2	Lack of clinical effectiveness data for NHS patients for who currently receive IO therapy	2.3.2, 3.7.1 and 3.8
Issue 3	Both investigator-assessed and BICR-assessed PFS data used in NMAs	3.4.1, 3.7.1, 3.7.3 and 3.8
Issue 4	Uncertainties around FP NMA model selection to estimate time-varying HRs	3.7.3 and 3.8
Issue 5	Difficulties interpreting PFS and OS FP NMA results	3.7.3, 3.7.4 and 3.8
Issue 6	Clinical effectiveness of nivolumab-relatlimab versus pembrolizumab: data limitations	2.3.4, 3.7.1, 3.7.3 and 3.8
Issue 7	Limited generalisability of company cost effectiveness results to NHS patients for whom IO combination therapy is not suitable or acceptable	6.1 and 6.12
Issue 8	Uncertain RELATIVITY-047 trial long-term OS data	6.2, 6.3 and 6.12
Issue 9	Implausible proportions of patients reaching background mortality after progression (nivolumab-relatlimab versus nivolumab+ipilimumab and versus pembrolizumab)	6.2, 6.3 and 6.12
Issue 10	Uncertain pembrolizumab NMA results: consequences for cost effectiveness results	6.4.2 and 6.12
Issue 11	A 2-year treatment stopping rule should not have been applied	6.5
Issue 12	Inappropriate AE costs and disutilities applied for patients treated with nivolumab+ipilimumab	6.7
Issue 13	Company subsequent treatment assumptions	6.6 and 6.12
Issue 14	Nivolumab-relatlimab has an EU marketing authorisation that limits use to patients with PD-L1 tumour expression <1%	2.2.2, 2.3.2, 2.3.6, 2.3.7 and 3.8

BICR=blinded independent central review; EU=European Union; FP=fractional polynomial; HR=hazard ratio; IO=immune-oncology; NMA=network meat-analysis; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained. The company model generates cost effectiveness results for the comparison of nivolumab-relatlimab versus nivolumab, versus nivolumab+ipilimumab and versus pembrolizumab. The EAG assumptions that have the biggest effects on costs and QALYs vary by comparator.

1.3 *The decision problem: summary of the EAG's key issues*

Issue 1 Lack of clinical trial evidence for patients aged 12 to 18 years

Report section	2.2.3, 2.3.2, 3.1 and 3.8
Description of issue and why the EAG has identified it as important	The population specified in the final scope issued by NICE included children and young adults aged 12 to 18 years. Patients aged ≥12 years were eligible for inclusion in the RELATIVITY-047 trial; however, all patients enrolled in the RELATIVITY-047 trial were aged >20 years. The company's systematic review identified studies of adults (aged ≥18 years). The eligibility criteria used may have affected the completeness of the evidence identified to inform this appraisal as studies of patients aged 12 to 18 years would not have been identified. At clarification, the company confirmed that there is no clinical trial evidence to support nivolumab-relatlimab as a treatment for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma. Clinical advice to the EAG is that there is no established NHS treatment pathway for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma. Only pembrolizumab is licensed for patients aged ≥12 years.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	None. If the NICE AC considers that patients aged 12 to 18 years and patients aged ≥18 years have similar melanoma pathophysiology and treatment responses, then the clinical effectiveness evidence for patients aged ≥18 years can be used as a proxy for patients aged 12 to 18 years.

AC=Appraisal Committee; EAG=External Assessment Group; NICE=National Institute for Health and Care Excellence

Issue 2 Lack of clinical effectiveness data for NHS patients who currently receive IO monotherapy

Report section	2.3.2, 3.7.1 and 3.8
Description of issue and why the EAG has identified it as important	In NG14, it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • for whom IO combination therapy (currently only nivolumab+ipilimumab) is suitable and acceptable, receive nivolumab+ipilimumab • for whom nivolumab+ipilimumab is **not** suitable or acceptable, receive pembrolizumab or nivolumab. The EAG considers that all NHS patients treated with nivolumab+ipilimumab, and some patients treated with pembrolizumab or nivolumab, are patients for whom nivolumab-relatlimab would be suitable. It is unclear whether the available trial evidence should be used to inform decision-making for the population for whom nivolumab+ipilimumab is not suitable or acceptable as the RELATIVITY-047 trial, CheckMate 067 trial and CheckMate 069 trial only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion.

EAG=External Assessment Group; IO=immuno-oncology; NG=NICE Guidance

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 3 Using both investigator-assessed and BICR-assessed PFS data in NMAs

Report section	3.4.1, 3.7.1, 3.7.3 and 3.8
Description of issue and why the EAG has identified it as important	All the company NMAs (estimating constant and time-varying HRs) used BICR-assessed PFS data from the RELATIVITY-047 trial and investigator-assessed PFS from the other three trials. The EAG considers that this approach was not appropriate because BICR-assessed PFS and median investigator-assessed PFS differed in the nivolumab arm ([redacted] months and [redacted] months, respectively). The company also stated (Clarification Question A5) that BICR-assessed PFS and investigator-assessed PFS were separate outcomes of the RELATIVITY-047 trial (i.e., the primary outcome for which the trial was powered, and an exploratory outcome for which the trial was not powered, respectively). Therefore, the company PFS NMAs, which included data from both BICR-assessed PFS and investigator-assessed PFS, are inappropriate and will be impacted by the heterogeneity introduced by the different outcome definitions and assessment methods used. Therefore, only investigator-assessed PFS should have been used for the PFS NMAs.
What alternative approach has the EAG suggested?	The EAG conducted a constant HR NMA using investigator-assessed PFS data from all four trials.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates of using time-varying HRs using investigator-assessed PFS data from all four trials is unknown. Using investigator-assessed PFS data from all four trials, EAG exploratory deterministic analysis results show that treatment with nivolumab-relatlimab dominates nivolumab+ipilimumab and pembrolizumab (PAS prices for nivolumab-relatlimab and nivolumab+ipilimumab, and list prices for pembrolizumab).
What additional evidence or analyses might help to resolve this key issue?	If time-varying HRs are preferred to constant HRs, then FP NMAs using investigator-assessed PFS are required.

BICR=blinded independent central review; EAG=External Assessment Group; FP=fractional polynomial; HR=hazard ratio; NMA=network meta-analysis; PFS=progression-free survival

Issue 4 Uncertainties around FP NMA model selection to estimate time-varying HRs

Report section	3.7.3 and 3.8
Description of issue and why the EAG has identified it as important	Model fit was assessed according to the DIC statistic followed by assessment of the fit of FP curves to K-M data and clinical plausibility of extrapolation estimates. While DIC statistics allow for comparison of the different model fits, they do not provide information about whether a model is a good fit to the data or whether the model estimates are clinically plausible. FP models with clinically implausible survival estimates were not considered for use in the base case analysis.
What alternative approach has the EAG suggested?	The EAG considers that FP model selection should primarily be based on clinical plausibility of model estimates, including projections of trial data, before model fit statistics are considered.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Presentation of all PFS and OS FP NMAs that generate clinically plausible results and the corresponding DIC statistics would be informative. Together, this information could be used to ensure that the most appropriate FP model, of all FP models considered, is selected.

CrI=credible interval; DIC=Deviance Information Criterion; EAG=External Assessment Group; FP=fractional polynomial; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival

Issue 5 Difficulties interpreting PFS and OS FP NMA results

Report section	3.7.3, 3.7.4 and 3.8
Description of issue and why the EAG has identified it as important	The company conducted FP NMAs, constant HR NMAs and adjusted ITCs to compare nivolumab-relatlimab versus relevant comparators. FP NMA results can be difficult to interpret, particularly when assessing the long-term survival estimate results generated for time periods beyond included trial follow-up times. The 95% CrIs around the time-varying HRs reflect the amount of data available overall and not the number of patients providing data at each timepoint. Therefore, the EAG considers that it is not appropriate to infer statistical significance (or lack of) from the FP NMAs 95% CrIs.
What alternative approach has the EAG suggested?	The EAG is not aware of existing methods that can be used to adjust FP NMA 95% CrIs to reflect the number of patients providing data at each timepoint. The EAG considers the best available evidence provided by the company for comparisons between treatments for PFS and OS are: • nivolumab-relatlimab versus nivolumab: RELATIVITY-047 trial • nivolumab-relatlimab versus nivolumab+ipilimumab: adjusted ITCs • nivolumab-relatlimab versus pembrolizumab: EAG constant HR NMAs (the reliability of these results is limited due to the violation of the PH assumption for the trials included in the constant HR NMAs). See also Issue 6.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to	None

resolve this key issue?	

CrI=credible interval; EAG=External Assessment Group; FP=fractional polynomial; HR=hazard ratio; ITC=indirect treatment comparison; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival; PH=proportional hazard

Issue 6 Clinical effectiveness of nivolumab-relatlimab versus pembrolizumab: data limitations

Report section	2.3.4, 3.7.1, 3.7.3 and 3.8
Description of issue and why the EAG has identified it as important	KEYNOTE-006 trial efficacy data were available for treatment naïve patients; however, safety data were only available for the overall population, which included previously treated patients (34%). The EAG has methodological concerns about the company constant HR NMAs and FP NMAs. The EAG is satisfied that the company's adjusted ITCs are methodologically robust; however, KEYNOTE-006 trial pembrolizumab PLD are not available and therefore pembrolizumab was not included as a comparator in these analyses. The EAG considers that the EAG constant HR NMAs provide the most informative NMA results for the comparison of nivolumab-relatlimab versus pembrolizumab.
What alternative approach has the EAG suggested?	None. PLD from the KEYNOTE-006 trial would be required to perform an adjusted ITC of nivolumab-relatlimab compared to pembrolizumab; these data are not publicly available.
What is the expected effect on the cost effectiveness estimates?	Unknown. See Issue 9.
What additional evidence or analyses might help to resolve this key issue?	Seek advice from clinicians on the relative clinical effectiveness of nivolumab-relatlimab versus pembrolizumab.

AC=Appraisal Committee; EAG=External Assessment Group; HR=hazard ratio; IO=immuno-oncology; ITC=indirect treatment comparison; NICE=National Institute for Health and Care Excellence; NMA=network meta-analysis; PLD=patient level data

1.5 *The cost effectiveness evidence: summary of the EAG's key issues*

Issue 7 Limited generalisability of company cost effectiveness results to NHS patients for whom IO combination therapy is not suitable or acceptable

Report section	6.1 and 6.12
Description of issue and why the EAG has identified it as important	Clinical advice to the EAG is that between 30% and 50% of NHS patients with untreated unresectable or metastatic melanoma are treated with pembrolizumab (or nivolumab); for these patients, an IO combination therapy (currently only nivolumab+ipilimumab) is not suitable or acceptable. The EAG considers that the company and EAG cost effectiveness results only relate to patients for whom IO combination therapy is suitable and acceptable (nivolumab-relatlimab and nivolumab+ipilimumab).
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice.

EAG=External Assessment Group; IO=immuno-oncology

Issue 8 Uncertain RELATIVITY-047 trial long-term OS data

Report section	6.2, 6.3 and 6.12
Description of issue and why the EAG has identified it as important	The company has modelled OS (including the proportion of patients who are 'cured') in a way that means that patients treated with nivolumab-relatlimab survive longer than patients treated with nivolumab+ipilimumab, nivolumab or pembrolizumab; the evidence to support the modelled OS gains is uncertain.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice.

EAG=External Assessment Group; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival

Issue 9 Implausible proportions of patients reaching background mortality after progression (nivolumab-relatlimab versus nivolumab+ipilimumab and versus pembrolizumab)

Report section	6.2, 6.3 and 6.12
Description of issue and why the EAG has identified it as important	Company base case results generate implausible differences in the proportions of patients treated with nivolumab-relatlimab and the proportions treated with nivolumab+ipilimumab and pembrolizumab, who achieve background mortality after progression.
What alternative approach has the EAG suggested?	The EAG used the following PFS and OS estimates for each comparator: • nivolumab+ipilimumab: company adjusted ITCs (using investigator-assessed PFS data) • pembrolizumab: RELATIVITY-047 trial nivolumab data
What is the expected effect on the cost effectiveness estimates?	Using PAS prices for all company assets, the EAG generated deterministic analysis results. For the comparison of nivolumab-relatlimab: • versus nivolumab+ipilimumab: nivolumab-relatlimab dominates • versus pembrolizumab: nivolumab-relatlimab dominates
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice.

EAG=External Assessment Group; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival

Issue 10 Uncertain pembrolizumab NMA results: consequences for cost effectiveness results

Report section	6.4.2 and 6.12
Description of issue and why the EAG has identified it as important	Due to pembrolizumab PLD not being available, pembrolizumab could not be included as a comparator in the company adjusted ITCs. Clinical advice to the EAG is that the clinical effectiveness and safety profiles of pembrolizumab and nivolumab are very similar.
What alternative approach has the EAG suggested?	In line with company scenario 6, the EAG has run an alternative scenario in which the PFS/OS for pembrolizumab has been set equal to the PFS/OS for nivolumab (RELATIVITY-047 trial data).
What is the expected effect on the cost effectiveness estimates?	Using PAS prices for nivolumab-relatlimab and list prices for pembrolizumab, both the company scenario analysis and EAG alternative scenario results show that treatment with nivolumab-relatlimab dominates.
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice.

EAG=External Assessment Group; ITC=indirect treatment comparison; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; PLD=patient level data

Issue 11 A 2-year treatment stopping rule should not have been applied

Report section	6.5
Description of issue and why the EAG has identified it as important	The company has assumed that all treatment with all IO therapies stops at 2 years (based on clinical advice and NICE melanoma HEMR). However, a treatment stopping rule was not implemented in the RELATIVITY-047 trial and is not specified in the EU marketing authorisation for nivolumab-relatlimab. In addition, no stopping rules were specified in the NICE recommendations for nivolumab, pembrolizumab or nivolumab+ipilimumab as treatments for advanced melanoma. The EAG therefore considers that a 2-year treatment stopping rule should not have been implemented in the company model.
What alternative approach has the EAG suggested?	The EAG has removed the 2-year treatment stopping rule. Removing the treatment stopping rule means that the company approach to modelling TTD for patients treated with nivolumab+ipilimumab needs to be altered to be in line with the approach used to model TTD for the other treatments.
What is the expected effect on the cost effectiveness estimates?	Using PAS prices for company assets and the list price for pembrolizumab, the EAG has generated deterministic analysis results. For the comparison of nivolumab-relatlimab: • versus nivolumab: £33,876 per QALY gained • versus nivolumab+ipilimumab: £50,288 per QALY gained • versus pembrolizumab: nivolumab-relatlimab dominates
What additional evidence or analyses might help to resolve this key issue?	None

EAG=External Assessment Group; TTD=time to treatment discontinuation; IO=immune-oncology; NICE=National Institute for Health and Care Excellence; PAS=Patient Access Scheme; QALY=quality adjusted life year

Issue 12 Inappropriate AE costs and disutilities applied for patients treated with nivolumab+ipilimumab

Report section	6.7
Description of issue and why the EAG has identified it as important	Patients treated with nivolumab+ipilimumab only receive ipilimumab for three model cycles (four treatment cycles). However, the company has applied nivolumab+ipilimumab AE costs and disutilities even when patients are only receiving nivolumab monotherapy.
What alternative approach has the EAG suggested?	The EAG has assumed that, in the model, once treatment with ipilimumab has ceased, only the costs and disutilities associated with nivolumab are applied.
What is the expected effect on the cost effectiveness estimates?	The effect of the EAG amendment to nivolumab+ipilimumab AE costs and disutilities is only important if the 2-year stopping rule is removed.
What additional evidence or analyses might help to resolve this key issue?	AE data for the induction and maintenance treatment periods of nivolumab+ipilimumab from the CheckMate 067 trial.

AE=adverse event; EAG=External Assessment Group

Issue 13 Company subsequent treatment assumptions

Report section	6.6 and 6.12
Description of issue and why the EAG has identified it as important	The EAG has concerns about the way that the company has modelled subsequent treatments. These concerns relate to: • the proportions who received subsequent treatments • the assumption that patients treated with nivolumab-relatlimab would not receive ipilimumab as a subsequent treatment
What alternative approach has the EAG suggested?	The EAG has: • changed the proportions of patients who receive subsequent treatments • assumed that some patients treated with nivolumab-relatlimab will receive ipilimumab as a subsequent treatment
What is the expected effect on the cost effectiveness estimates?	Using PAS prices for company assets and the list price for pembrolizumab, the EAG generated deterministic analysis results. For the comparison of nivolumab-relatlimab: • versus nivolumab: £34,038 per QALY gained • versus nivolumab+ipilimumab: £16,319 per QALY gained • versus pembrolizumab: nivolumab-relatlimab dominates
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice.

EAG=External Assessment Group; PAS=Patient Access Scheme; QALY=quality adjusted life year

1.6 *Other key issues: summary of the EAG's view*

Issue 14 Nivolumab-relatlimab has an EU marketing authorisation that limits use to patients with PD-L1 tumour expression <1%

Report section	2.2.2, 2.3.2, 2.3.6, 2.3.7 and 3.8
Description of issue and why the EAG has identified it as important	UK nivolumab-relatlimab marketing authorisation has not yet been granted. The US FDA has approved nivolumab-relatlimab for the treatment of patients ≥12 years with unresectable or metastatic melanoma. However, in the EU, nivolumab-relatlimab is only approved "for the first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression <1%." The company has presented RELATIVITY-047 trial subgroup analyses results by level of PD-L1 tumour expression for nivolumab-relatlimab versus nivolumab. In both the nivolumab-relatlimab and nivolumab arms of the RELATIVITY-047 trial, median BICR-assessed PFS was [redacted] in patients with PD-L1 tumour expression <1% than in the ITT population. The company did not provide clinical effectiveness results for nivolumab-relatlimab versus nivolumab+ipilimumab or versus pembrolizumab, or cost effectiveness results versus any comparator, from analyses by PD-L1 expression level.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The UK MHRA decision is expected in [redacted]. If it is stipulated in the marketing authorisation that treatment with nivolumab-relatlimab depends on PD-L1 tumour expression, then the following analyses would be required: • clinical effectiveness analyses by PD-L1 tumour expression level for nivolumab-relatlimab versus nivolumab+ipilimumab and versus pembrolizumab • cost effectiveness analyses by PD-L1 tumour expression level for nivolumab-relatlimab versus nivolumab, versus nivolumab+ipilimumab and versus pembrolizumab.

BICR=blinded independent central review; EU=European Union; FDA=Food and Drugs Administration; ITT=intention-to-treat; MHRA=UK Medicines and Healthcare products Regulatory Agency; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival

1.7 *Summary of EAG's preferred assumptions and resulting ICERs*

The following deterministic cost effectiveness results have been generated using PAS prices for all company assets.

Table B EAG revisions to company base case: nivolumab-relatlimab versus nivolumab

Scenario/EAG revisions*	Incremental		ICER
	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	**£20,426**
R1) RELATIVITY-047 trial PFS (investigator-assessed)	[redacted]	[redacted]	£18,049
R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS			
R3) Constant HRs from the company adjusted ITC for nivolumab+ipilimumab			
R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)			
R5) TTD constraint (≤ PFS) removed	[redacted]	[redacted]	£17,848
R6a) 2 year stopping rules for IO therapies removed	[redacted]	[redacted]	£33,876
R6b) 2 year stopping rule removed: plus nivolumab+ipilimumab K-M used up to [redacted] years and nivolumab TTD hazards applied thereafter			
R7) Alternative subsequent treatment cost calculations	[redacted]	[redacted]	£34,038
R8) EAG change to IV administration costs	[redacted]	[redacted]	£19,725
B. EAG alternative scenario (R1, R5, R6a, R7, R8)	[redacted]	[redacted]	**£44,404**
C. EAG exploratory analyses			
R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD			
R10) General population utility from point of background mortality hazards	[redacted]	[redacted]	£19,351
R11) EAG combined exploratory analysis			

EAG=External Assessment Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; IO=immune-oncology; ITC=indirect treatment comparison; IV=intravenous; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation; QALY=quality adjusted life year
Source: Section 6, Table 50

Table C EAG revisions to company bas6e case: nivolumab-relatlimab versus nivolumab+ipilimumab

Scenario/EAG revisions*	Incremental		ICER
	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	**NIV-REL dominates**
R1) RELATIVITY-047 trial PFS (investigator-assessed)	[redacted]	[redacted]	NIV-REL dominates
R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS			
R3) Constant HRs from the company adjusted ITC for nivolumab+ipilimumab[a]	[redacted]	[redacted]	NIV-REL dominates
R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)	[redacted]	[redacted]	NIV-REL dominates
R5) TTD constraint (≤ PFS) removed	[redacted]	[redacted]	NIV-REL dominates
R6a) 2 year stopping rules for IO therapies removed	[redacted]	[redacted]	NIV-REL dominates
R6b) 2 year stopping rule removed; plus nivolumab+ipilimumab K-M data used up to [redacted] years and nivolumab TTD hazards applied thereafter	[redacted]	[redacted]	£49,936
R7) Alternative subsequent treatment cost calculations	[redacted]	[redacted]	£16,319
R8) EAG change to IV administration costs	[redacted]	[redacted]	NIV-REL dominates
B. EAG alternative scenario (R1, R3-R5, R6a-R8)	[redacted]	[redacted]	**£118,253**
C. EAG exploratory analyses			
R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD	[redacted]	[redacted]	NIV-REL dominates
R10) General population utility from point of background mortality hazards	[redacted]	[redacted]	NIV-REL dominates
R11) EAG combined exploratory analysis (R1, R4-R6a, R7-R9)	[redacted]	[redacted]	£2,974,310

[a] PFS constant HRs from the company adjusted ITC for investigator-assessed PFS
EAG=External Assessment Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; IO=immune-oncology; ITC=indirect treatment comparison; IV=intravenous; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation; QALY=quality adjusted life year
Source: Section 6, Table 52

Table D EAG revisions to company base case: nivolumab-relatlimab versus pembrolizumab

Scenario/EAG revisions*	Incremental		ICER
	Costs	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	**NIV-REL dominates**
R1) RELATIVITY-047 trial PFS (investigator-assessed)	[redacted]	[redacted]	NIV-REL dominates
R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS	[redacted]	[redacted]	NIV-REL dominates
R3) Constant HRs from the company adjusted ITC for nivolumab+ipilimumab			
R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)			
R5) TTD constraint (≤ PFS) removed	[redacted]	[redacted]	NIV-REL dominates
R6a) 2 year stopping rules for IO therapies removed	[redacted]	[redacted]	NIV-REL dominates
R6b) 2 year stopping rule removed; plus nivolumab+ipilimumab K-M data used up to *** years and nivolumab TTD hazards applied thereafter			
R7) Alternative subsequent treatment cost calculations	[redacted]	[redacted]	NIV-REL dominates
R8) EAG change to IV administration costs	[redacted]	[redacted]	NIV-REL dominates
B. EAG alternative scenario (R1-R2, R5, R6a, R7-R8)	[redacted]	[redacted]	**NIV-REL dominates**
C. EAG exploratory analyses			
R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD			
R10) General population utility from point of background mortality hazards	[redacted]	[redacted]	NIV-REL dominates
R11) EAG combined exploratory analysis			

EAG=External Assessment Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; IO=immune-oncology; ITC=indirect treatment comparison; IV=intravenous; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation; QALY=quality adjusted life year

Source: Section 6,

Table 54

For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.1 to Section 6.6.

2. INTRODUCTION AND BACKGROUND

2.1 *Introduction*

This appraisal focuses on nivolumab-relatlimab (brand name: Opdualag) as a treatment option for patients aged 12 years and older with previously untreated unresectable or metastatic melanoma (i.e., Stage III or Stage IV disease).

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B (version 2.0, dated 28 April 2023), which is the company's full evidence submission. Additional evidence was provided by the company at the clarification stage.

2.2 *Background*

2.2.1 Melanoma

Melanoma is a form of skin cancer. In the UK, melanoma is the third most common skin cancer (behind basal cell and squamous cell carcinomas)[1] and the fifth most common cancer. Melanoma accounted for 4% of all new cancer cases between 2016 and 2018;[2] during this period, most new cases of melanoma were in people aged 70 to 74 years (Table 1). For people younger than 55 years, there were more new cases in females than in males, and for people ≥60 years, there were more new cases in males than females. When considering all ages, the number of new cases of melanoma was evenly distributed by sex. Most new cases (99.8%) were in adults aged ≥20 years.

Table 1 Average number of new cases of melanoma (all stages) per year in the UK (2016-18)

Age range, years	Females	Males	Age range, years	Females	Males
<15	3	3	55 to 59	736	707
15 to 19	19	10	60 to 64	730	816
20 to 24	95	38	65 to 69	903	1,073
25 to 29	210	105	70 to 74	971	1,216
30 to 34	331	174	75 to 79	743	1,069
35 to 39	392	213	80 to 84	626	866
40 to 44	481	270	85 to 89	434	538
45 to 49	654	453	≥90	263	234
50 to 54	769	599	All ages	8,360	8,384

Source: Cancer research UK[2]

Despite making up less than 5% of all cases of skin cancer, melanoma accounts for 65% of all skin cancer-related deaths.[1] Survival rates differ depending on the stage at diagnosis; in England, patients with Stage IV disease have the poorest prognosis (Table 2).[3] Survival rates are reported to be slightly higher for women than for men.[3,4]

Table 2 Net survival (%) by stage at diagnosis for people with melanoma aged ≥15 years diagnosed in England (2013-2017)

Stage	Number of patients	Survival type	1-year net survival, %	5-year net survival, %
I	40,058	Non-standardised	100.6	99.6
		Age-standardised	100.4	99.6
II	12,174	Non-standardised	97.1	75.0
		Age-standardised	98.2	80.4
III	3752	Non-standardised	93.3	67.6
		Age-standardised	94.7	70.6
IV	1447	Non-standardised	50.8	25.3
		Age-standardised	53.0	NE
Unstageable	9	Non-standardised	NE	NE
		Age-standardised	NE	NE
Unknown/ missing	5216	Non-standardised	92.7	74.6
		Age-standardised	95.4	82.3
All stages combined	62,656	Non-standardised	97.7	89.2
		Age-standardised	98.2	91.3

NE=not estimable
Source: Office for National Statistics and Public Health England[3]

The company highlighted that the introduction of immuno-oncology (IO) therapies for treating melanoma has increased survival rates. In the CheckMate 067[5] trial (which commenced in 2016 and included 93.2% patients with Stage IV untreated melanoma), 5-year survival rates for patients treated with ipilimumab (26%), nivolumab (44%) and nivolumab+ipilimumab (52%) were higher than those reported for patients diagnosed with Stage IV melanoma in England between 2013 and 2017 (Table 2).

2.2.2 Nivolumab-relatlimab

Nivolumab is a programmed death-1 (PD-1) receptor-blocking monoclonal antibody and relatlimab is a human immunoglobulin G4 lymphocyte-activation gene 3 (LAG-3) blocking antibody.[6,7] PD-1 and LAG-3 are two distinct inhibitory immune checkpoints.[6] Nivolumab binds to the PD-1 and blocks interaction with its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2), to reduce PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response.[8] Relatlimab binds to LAG-3 and acts to restore the effector function of dysfunctional T-cells while promoting cytokine secretion (CS, p13). The combination of nivolumab and relatlimab results in increased T-cell

activation compared to the activity of either antibody alone, resulting in an improved anti-tumour immune response.[6-8]

Nivolumab-relatlimab is a fixed-dose combination (FDC) of nivolumab and relatlimab prepared as a solution concentrate for infusion in a single use vial.[6,7] In contrast, treatment with nivolumab+ipilimumab (the only other IO combination therapy currently available for patients with unresectable or metastatic melanoma) is administered as two separate infusions over 90 minutes.

As highlighted in the CS (Table 2):

- nivolumab-relatlimab is prepared in normal saline and administered as an intravenous (IV) infusion over 30 minutes
- the recommended dose for patients aged 12 to 18 years who weigh ≥30kg and all patients aged ≥18 years is 480mg nivolumab and 160mg relatlimab every 4 weeks (Q4W)
- dose escalations/reductions are not recommended; for safety and tolerability reasons, individuals may require dosing delay or discontinuation.

Nivolumab-relatlimab may be infused undiluted or diluted with either 9mg/mL (0.9%) sodium chloride (normal saline) or 50mg/mL (5%) glucose solution prior to administration.[6-8]

On 18 March 2022, the US Food and Drug Administration (FDA) approved nivolumab-relatlimab for the treatment of patients ≥12 years with unresectable or metastatic melanoma.[8] On 21 July 2022, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for a narrower indication than the FDA, namely "for the first line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression <1%."[7] The nivolumab-relatlimab application for marketing authorisation from the UK Medicines and Healthcare products Regulatory Agency (MHRA) is ongoing (CS, Table 2). The MHRA decision is expected in [redacted]. The proposed MHRA indication is: [redacted].[6] The company's proposed indication is [redacted].

2.2.3 Overview of current service provision

The company has presented information outlining the current NHS treatment pathway and the positioning of nivolumab-relatlimab, should nivolumab-relatlimab be recommended by NICE (CS, Figure 2). The company's pathway was informed by the NICE melanoma assessment and management guidelines (NG14)[9] and clinical advice.[10] In NG14,[9] the evidence showed that IO therapies were more clinically effective and cost effective than targeted therapies (i.e.,

BRAF inhibitors and mitogen-activated extracellular signal-regulated kinase [MEK] inhibitors) and that IO combination therapy (nivolumab+ipilimumab) was more clinically effective and cost effective than IO monotherapies. However, it was also noted that the toxicity risk associated with IO therapies was greater than the toxicity risk associated with targeted therapies and that the toxicity risk associated with IO combination therapy (nivolumab+ipilimumab) was greater than the toxicity risk associated with IO monotherapies (nivolumab and pembrolizumab). In NG14,[9] it is therefore recommended that the following factors should be considered when making treatment decisions:

- comorbidities and performance status
- risk of treatment toxicity
- whether potential treatment toxicity will be tolerated
- presence of symptomatic brain metastases
- tumour biology (e.g., high disease burden, rapid progression, lactate dehydrogenase level).

In NG14,[9] treatment with nivolumab+ipilimumab is the preferred first-line treatment for adult patients with previously untreated unresectable or metastatic melanoma if suitable and acceptable for patients based on the above listed factors. If treatment with nivolumab+ipilimumab is unsuitable or is not acceptable (e.g., due to potential toxicity) for patients, then, in the first-line setting, patients should be treated with pembrolizumab or nivolumab monotherapy. Although both nivolumab and pembrolizumab are PD-L1 inhibitors, patients with untreated unresectable or metastatic melanoma are not tested for PD-L1 tumour expression level; clinical advice to the EAG is that PD-L1 tumour expression level is not considered clinically relevant for treating advanced melanoma.

Clinical advice to the company[10] is that in current NHS clinical practice, nivolumab+ipilimumab is the first-line treatment for approximately [redacted] of patients with previously untreated unresectable or metastatic melanoma and that approximately [redacted] and [redacted] of patients are treated with pembrolizumab monotherapy and nivolumab monotherapy, respectively. Clinical advice to the EAG is that there is likely to be geographical variation in these proportions due to socioeconomic status, capacity and clinician familiarity with regimens (nivolumab+ipilimumab: 50% to 70%; pembrolizumab: 30% to 50% and nivolumab: ≤1%). Clinical advice to the EAG is that pembrolizumab monotherapy is preferred to nivolumab monotherapy because pembrolizumab has a less intensive dosing regimen (400mg every 6 weeks [Q6W]) than nivolumab (480mg Q4W).

The company's positioning of nivolumab-relatlimab (CS, Figure 2) suggests that, if recommended by NICE, nivolumab-relatlimab would be available as a first-line IO therapy for adult patients with previously untreated unresectable or metastatic melanoma for whom nivolumab+ipilimumab is unsuitable.

The EAG notes that nivolumab+ipilimumab,[11] nivolumab[12] and pembrolizumab[13] are only recommended by NICE for **adults** with previously untreated unresectable or metastatic melanoma. Clinical advice to the EAG is that there is no established NHS treatment pathway for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma; these patients would be managed by oncologists in paediatric cancer centres with input from adult melanoma specialists. In NG14,[9] the guideline committee considered that treatment should not differ between children and adults and that recommendations also apply to children and young people. The EAG notes that only pembrolizumab is licensed for patients aged ≥12 years[14] but that untreated unresectable or metastatic melanoma is rare in patients aged 12 to 18 years; patients aged <20 years account for only 0.2% of new melanoma cases (all cancer stages) each year in the UK.[2]

2.3 *Critique of company's definition of decision problem*

A summary of the decision problem outlined in the final scope[15] issued by NICE and addressed by the company is presented in Table 3. Each parameter is discussed in more detail in the text following Table 3 (Section 2.3.1 to Section 2.3.8).

Table 3 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	People aged 12 years and older with previously untreated unresectable or metastatic melanoma	As per final scope	Largely as per NICE scope. The RELATIVITY-047 trial,[16] CheckMate 067 trial[17] and CheckMate 069 trial[18] only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable. It is unclear whether the available trial evidence should be used to inform decision-making for patients for whom IO combination therapy is not suitable. Patients aged ≥12 years were eligible for inclusion in the RELATIVITY-047 trial but only patients aged ≥20 years were enrolled. There is no clinical trial evidence for patients aged 12 to 18 years (Clarification Question A3)
Intervention	Nivolumab-relatlimab	As per final scope	As per NICE scope
Comparator(s)	• Nivolumab • Nivolumab with ipilimumab • Pembrolizumab	As per final scope	As per NICE scope
Outcomes	The outcome measures to be considered include: • PFS • OS • ORR • AEs • HRQoL	As per final scope	As per NICE scope

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The economic modelling should include the costs associated with diagnostic testing for PD-L1 expression in people with melanoma who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test	No PD-L1 testing is included in the economic analysis. PD-L1 testing is not considered for treatment decision making in previously untreated unresectable or metastatic melanoma	Largely as specified in the NICE scope. The EAG agrees with the company that the cost associated with PD-L1 diagnostic testing should not have been included in the analysis
Subgroups	If the evidence allows the following subgroups will be considered: • PD-L1 expression (≥1% or <1%) • *BRAF* V600 mutation status	Pre-planned subgroup analyses that include PD-L1 and BRAF subgroups are presented in the clinical section only; these subgroups are not considered relevant for cost-effectiveness analyses. The current management pathway does not consider PD-L1 or *BRAF* status for first-line treatment decisions. This will not change with the introduction of nivolumab-relatlimab	The company has provided clinical effectiveness results from the RELATIVITY-047 trial for nivolumab-relatlimab versus nivolumab for subgroups by PD-L1 expression level and by BRAF V600 mutation status for PFS, OS and ORR

AEs=adverse events; HRQoL=health-related quality of life; IO=immuno-oncology; NICE=National Institute for Health and Care Excellence; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year
Source: Final scope issued by NICE and CS, Table 1

2.3.1 Source of direct clinical effectiveness data

The primary source of direct clinical effectiveness evidence presented by the company was the RELATIVITY-047[16] trial. The RELATIVITY-047 trial is a phase II/III, multicentre, international, double-blind randomised controlled trial (RCT) comparing nivolumab-relatlimab (N=355) versus nivolumab (N=359) as treatments for patients with previously untreated metastatic or unresectable melanoma.

2.3.2 Population

The population addressed by the company largely matches the population specified in the final scope issued by NICE. The EAG notes that the population specified in the final scope issued by NICE differs to the population specified in the company proposed MHRA licence (i.e., [redacted] versus [redacted]) and the European Union approved marketing authorisation (i.e., [redacted] versus [redacted]).

In NG14,[9] it is recommended that NHS patients with untreated unresectable or metastatic melanoma:

- for whom IO combination therapy (currently only nivolumab+ipilimumab) is suitable and acceptable, receive nivolumab+ipilimumab
- for whom nivolumab+ipilimumab is **not** suitable or acceptable, receive pembrolizumab or nivolumab.

It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial[17] and CheckMate 069 trial[18]) should be used to inform decision-making for the population for whom nivolumab+ipilimumab is **not** suitable or acceptable as these trials only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable.

Clinical advice to the EAG is that the RELATIVITY-047 trial population is representative of adult patients with previously untreated metastatic or unresectable melanoma who are likely to be treated in NHS clinical practice and for whom an IO combination therapy is suitable and acceptable.

The population specified in the final scope issued by NICE includes children and young adults aged 12 years to 18 years. Patients aged ≥12 years were eligible for inclusion in the RELATIVITY-047 trial but all patients enrolled in the RELATIVITY-047 trial were aged >20 years. The company confirmed that there is no clinical trial evidence to support nivolumab-relatlimab as a treatment for patients aged 12 to 18 years with untreated unresectable or

metastatic melanoma (Clarification Question A3). The EAG considers that this is not unexpected as melanoma is uncommon in patients aged <20 years.[2]

2.3.3 Intervention

The company has presented evidence for nivolumab-relatlimab as per its proposed MHRA licensed indication.

In the RELATIVITY-047 trial, IV nivolumab-relatlimab was administered over 60 minutes (CS, Table 9), but in clinical practice, the company recommends a 30-minute infusion period.[7] As stated in the draft Summary of Product Characteristics (SmPC)[6] (p17): [redacted] Clinical advice to the EAG is that infusion duration is unlikely to affect efficacy or tolerability but that the first infusion may be administered over 60 minutes in case of allergic reactions, and if the patient tolerated the infusion, then subsequent infusions would be administered over 30 minutes.

2.3.4 Comparators

As specified in the final scope issued by NICE, the company has provided evidence for the comparisons of nivolumab-relatlimab versus nivolumab, versus nivolumab+ipilimumab and versus pembrolizumab for previously untreated metastatic or unresectable melanoma.

There was a lack of direct evidence comparing treatment with nivolumab-relatlimab versus nivolumab+ipilimumab and versus pembrolizumab. Using data from four trials,[16-19] the company carried out fixed effects (FE) network meta-analyses (NMAs) for progression-free survival (PFS), OS and safety outcomes (Grade 3 to 4 adverse events [AEs], Grade 3 to 4 treatment-related AEs [TRAEs], discontinuation due to AEs and discontinuation due to TRAEs).

The company also carried out adjusted indirect treatment comparisons (ITCs) to compare the effectiveness (OS and PFS) and safety of nivolumab-relatlimab versus nivolumab+ipilimumab using patient level data (PLD) from the RELATIVITY-047 and CheckMate 067[17] trials.

2.3.5 Outcomes

The outcomes specified in the final scope issued by NICE are standard outcomes used in oncology clinical trials and are the most important outcome measures for this appraisal.

The company provided results from the RELATIVITY-047 trial for nivolumab-relatlimab versus nivolumab for all outcomes included in the final scope issued by NICE. The company provided

indirect evidence for nivolumab-relatlimab versus nivolumab+ipilimumab and versus pembrolizumab for PFS, OS and safety outcomes but did not provide indirect evidence for objective response rate (ORR) or health-related quality of life (HRQoL).

2.3.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 40-year time period (which the company considered to be equivalent to a lifetime horizon) and costs were considered from an NHS and Personal Social Services (PSS) perspective.

The company did not provide cost effectiveness results from analyses by PD-L1 expression level or *BRAF* V600 mutation status. Clinical advice to the company was that neither the PD-L1 nor the *BRAF* status of tumours are currently considered when making first-line treatment decisions. Clinical advice to the EAG is that if the indication approved by the MHRA for nivolumab-relatlimab specifies PD-L1 tumour expression level, and if NICE recommends nivolumab-relatlimab for this indication, then PD-L1 tumour expression level will need to be measured.

2.3.7 Subgroups

The company has provided RELATIVITY-047 trial clinical effectiveness results (nivolumab-relatlimab versus nivolumab) for subgroups by PD-L1 expression level (≥1% or <1%, ≥5% or <5% and ≥10% or <10%,) and by *BRAF* V600 mutation status (mutant or wildtype) for PFS by blinded independent central review (BICR), OS and ORR. These were the subgroups specified in the final scope issued by NICE. The EAG notes that in the European Union, nivolumab-relatlimab is only licensed for patients "with tumour cell PD-L1 expression < 1%"[7] [redacted].

Clinical advice to the EAG is that melanoma tumours are not currently tested for PD-L1 status in NHS clinical practice. In NG14,[9] it is recommended that the BRAF status of patients should only be considered if IO combination therapy (currently only nivolumab+ipilimumab) or IO monotherapies are unsuitable or not acceptable. Clinical advice to the EAG is that *BRAF* status will affect first-line treatment decisions for a small proportion of patients (<5%) with rapidly progressing disease or symptomatic brain metastases; patients with *BRAF*-positive tumours may receive BRAF inhibitors rather than IO therapies in the first-line setting.

2.3.8 Other considerations

Nivolumab-relatlimab, nivolumab, pembrolizumab and ipilimumab are available to the NHS at confidential, discounted Patient Access Scheme (PAS) prices. The company has used the nivolumab-relatlimab, nivolumab and ipilimumab PAS prices and the pembrolizumab list price to generate the base case cost effectiveness results (company addendum).

The EAG agrees with the company (CS, Section B.1.4) that: “No equality considerations relating to the use of nivolumab-relatlimab have been identified or are anticipated.”

3. CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company in support of the use of nivolumab-relatlimab for patients with untreated unresectable or metastatic melanoma. The key components of the clinical effectiveness evidence presented in the CS are (i) direct evidence and (ii) indirect evidence.

3.1 *Critique of the methods of review(s)*

Full details of the methods used by the company to identify clinical effectiveness evidence of systemic therapies for patients with previously untreated unresectable or metastatic melanoma were presented in the CS (Appendix D). The company literature searches were comprehensive and were completed <6 months before the company's evidence submission to NICE. The EAG considers that the company's systematic review methods were appropriate for identifying studies of adults (aged ≥18 years); during clarification (Clarification Question A3), the company confirmed that there is no published clinical trial evidence to support nivolumab-relatlimab as a treatment for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma.

Table 4 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D, Table 2
Were appropriate sources searched?	Yes	CS, Appendix D, Section D.1.1
Was the timespan of the searches appropriate?	Yes	CS, Appendix D, Table 1
Were appropriate search terms used?	Yes	CS, Appendix D, Table 1
Were the eligibility criteria appropriate to the decision problem?	Mostly	CS, Appendix D, Table 2 The SLR eligibility criteria included studies of patients aged ≥18 years. The population specified in the final scope issued by NICE included people aged ≥12 years ([redacted]). The SLR eligibility criteria included studies of MEK inhibitors, BRAF inhibitors and chemotherapy in addition to the comparators listed in the final scope issued by NICE
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D, Section D.1.2
Was data extracted by two or more reviewers independently?	Yes	CS, Appendix D, Section D.1.2 One reviewer extracted data and the data were then checked by a second (independent) reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Section B.2.5 and CS, Appendix D, Section D.3
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix D, Section D.3
Were attempts to synthesise evidence appropriate?	Yes	NMAs and ITCs were performed. See Section 3.7.3 for a discussion of the company's methods and the EAG's critique of the indirect evidence syntheses

CS=company submission; EAG=External Assessment Group; ITCs=indirect treatment comparisons; MEK=mitogen-activated extracellular signal-regulated kinase; [redacted]; NICE=National Institute for Health and Care Excellence; NMAs=network meta-analyses; SLR=systematic literature review
Source: EAG in-house checklist

3.2 *Critique of main trial of the technology of interest, the company's analysis and interpretation*

3.2.1 Included trials

The company's systematic literature review (SLR) was broader (with regard to interventions) and narrower (with regard to population) than was required to address the decision problem described in the final scope issued by NICE. The company searched for studies of MEK inhibitors (binimetinib, cobimetinib and trametinib), BRAF inhibitors (dabrafenib, encorafenib and vemurafenib) and chemotherapy (dacarbazine), in addition to studies of nivolumab-relatlimab, nivolumab, nivolumab+ipilimumab and pembrolizumab and only included studies of patients ≥18 years.

The company SLR identified 16 RCTs[16-31] that provided clinical effectiveness evidence of systemic therapies for patients with previously untreated unresectable or metastatic melanoma. However, only four trials included either nivolumab-relatlimab or a comparator that is relevant to this appraisal:

- RELATIVITY-047 trial[16] (nivolumab-relatlimab versus nivolumab)
- CheckMate 067 trial[17](ipilimumab versus nivolumab+ipilimumab versus nivolumab)
- CheckMate 069 trial[18] (ipilimumab versus nivolumab+ipilimumab)
- KEYNOTE-006 trial[19] (ipilimumab versus pembrolizumab).

A list of the key RELATIVITY-047 trial reports and the publications for all four included trials[16-19] that informed this EAG report is presented in Table 5.

A description and critique of the RELATIVITY-047 trial are provided in Sections 3.3.1 to 3.3.5. Further information about the other three trials[17-19] is presented in Section 3.7.1.

Table 5 References to RELATIVITY-047 trial reports and key publications for the four trials included in the NMAs

Trial/ comparison	Reference	Description	Median follow-up (date)	Contribution to EAG report
RELATIVITY-047 Nivolumab-relatlimab vs nivolumab	Protocol[32]	RELATIVITY-047 trial Protocol (Amendment Number 03, version 8.0, date 23rd Nov 2020)	NA	Quality assessment of the RELATIVITY-047 trial (Section 3.3.4) Statistical approach adopted for the analysis of the RELATIVITY-047 trial (Section 3.3.5)
	Primary CSR[33]	Clinical study report for the March 2021 data cut. Primary analysis of BICR-assessed PFS, interim analyses of OS and ORR	13.2 months (Mar 2021)	Characteristics of RELATIVITY-047 trial patients (Section 3.3.2) Statistical approach adopted for the analysis of the RELATIVITY-047 trial (Section 3.3.5)
	CSR addendum 02[34]	Clinical study report for the Oct 2022 data cut. Updated analyses of efficacy and safety outcomes reported within the CS	[redacted] months (Oct 2022)	Efficacy outcomes (direct evidence, Section 3.4 and indirect evidence, Section 3.7) Safety outcomes (Direct evidence, Section 3.6 and indirect evidence, Section 3.7)
	TSAP for CSR addendum 02[35]	Statistical Analysis Plan for the updated analyses (version 6.0, date 25th May 2022 for Oct 2022 data cut)	[redacted] months (Oct 2022)	Quality assessment of the RELATIVITY-047 trial (Section 3.3.4) Statistical approach adopted for the analysis of the RELATIVITY-047 trial (Section 3.3.5)
	Schadendorf 2021[36]	Conference poster presentation of HRQoL outcomes (FACT-M and EQ-5D-3L)	13.2 months (Mar 2021)	Patient reported outcomes (Section 3.5)
	Tawbi 2022[16]	Primary publication of the RELATIVITY-047 trial (PFS final analysis)	13.2 months (Mar 2021)	NA
	Lipson 2021[37]	Conference presentation of PFS final analysis	13.2 months (Mar 2021)	NA
	Long 2022[38]	Conference abstract of updated PFS analysis, final analysis of OS and ORR	19.3 months (Oct 2021)	NA
CheckMate 067 Ipilimumab vs nivolumab+ ipilimumab vs nivolumab	Larkin 2015[17]	Primary publication of the CheckMate 067 trial (PFS final analysis)[a]	12.2 to 12.5 months[b] (Feb 2015)	Baseline patient characteristics (Section 3.7.1) and quality assessment of trials included in the NMAs (Section 3.7.2) Summary data for Grade 3 to 4 AEs NMA (Section 3.7.4 and Appendix 2, Section 8.2, Table 62)
	Larkin 2017[39]	Conference presentation of updated PFS and ORR analyses, final analysis of OS	28 months[c] (Sept 2016)	NA
	Wolchok 2017[40]	3-year analyses of PFS, OS, ORR and safety outcomes. Final analysis of OS	18.6 to 38 months[b] (May 2017)	NA
	Schadendorf 2017[41]	HRQoL outcomes (EORTC QLQ-C30 EQ-5D-3L and WPAI:GH)	up to week 55[d] (NR)	NA

Trial/ comparison	Reference	Description	Median follow-up (date)	Contribution to EAG report
	Hodi 2018[42]	4-year updated analyses of PFS, OS, ORR and safety outcomes	18.6 to 46.9 months[b] (May 2018)	NA
	Larkin 2019[5]	5-year updated analyses of PFS, OS, ORR and safety outcomes	18.6 to 54.6 months[b] (July 2019)	Summary data for ORR NMA (Appendix 2, Section 8.2, Table 63)
	Wolchok 2022[43]	Long term (6.5 years) updated analyses of PFS, OS and ORR	18.6 to 57.5 months[b] (Oct 2020)	Summary data for Grade 3 to 4 TRAEs, discontinuation due to AEs and TRAEs NMAs (Section 3.7.4 and Appendix 2, Section 8.2, Table 62)
	Hodi 2022[44]	Long term (7.5 years) updated analyses of PFS, OS, ORR and HRQoL outcomes	90 months[c] (Nov 2021)	Summary data for PFS (investigator-assessed) and OS NMAs (Section 3.7.4 and Appendix 2, Section 8.2, Table 61)
CheckMate 069 Ipilimumab vs nivolumab+ ipilimumab	Postow 2015[18]	Primary publication of the CheckMate 069 trial (ORR and PFS final analysis)[a]	11 months[c] (Jan 2015)	Baseline patient characteristics and quality assessment of trials included in the NMAs (Section 3.7.1 and Section 3.7.2)
	Hodi 2016[45]	OS final analysis	26.6 months (Feb 2016)	Summary data for PFS (investigator-assessed), OS, ORR, Grade 3 to 4 TRAEs, discontinuation due to AEs and TRAEs NMAs (Section 3.7.4 and Appendix 2, Section 8.2)
	Abernathy 2015[46]	Conference abstract of HRQoL outcomes (EORTC QLQ-C30 and EQ-5D-3L)	Up to 6 months (NR)	NA
KEYNOTE-006 Ipilimumab vs pembrolizumab	Robert 2015[19]	Primary publication of the KEYNOTE-006 trial. First interim analysis of PFS, ORR and safety outcomes. Second interim analysis of OS[a]	7.9 months (Sept 2014)	Baseline patient characteristics and quality assessment of trials included in the NMAs (Section 3.7.1 and Section 3.7.2)
	Schachter 2017[47]	OS final analysis	22.9 months (Dec 2015)	NA
	Petrella 2017[48]	HRQoL outcomes (EORTC QLQ-C30 and EQ-5D-3L)	Up to week 36 (NR)	NA
	Robert 2019[49]	5-year updated analyses of PFS, OS, ORR and safety outcomes	57.7 months (Dec 2018)	Summary data for PFS (investigator-assessed), OS, ORR, Grade 3 to 4 TRAEs, discontinuation due to AEs and TRAEs NMAs (Section 3.7.4 and Appendix 2, Section 8.2)

[a] Trial protocol and statistical analysis plan available as supplementary material
[b] Median follow-up reported by treatment arm only
[c] Minimum follow-up
[d] HRQoL outcome data collected up to week 79 but only data up to week 55 were included in longitudinal modelling
AE=adverse event; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-3L=European Quality of Life 5 Dimensions 3 Level Version; FACT-M=Functional Assessment of Cancer Therapy-Melanoma; HRQoL=health-related quality of life; NA=not applicable; NMA=network meta-analyses; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QLQ-C30=quality of life questionnaire core 30; TRAE=treatment related AE; vs=versus; WPAI=Work Productivity and Activity Impairment Questionnaire; GH=General Health

3.3 *Direct clinical effectiveness evidence*

Clinical effectiveness evidence for nivolumab-relatlimab (versus nivolumab) was only available from the RELATIVITY-047 trial.

3.3.1 Characteristics of the RELATIVITY-047 trial

The RELATIVITY-047 trial was a phase II/III, multicentre, international, double-blind RCT comparing nivolumab-relatlimab versus nivolumab as a treatment for patients with previously untreated metastatic or unresectable melanoma. As per the trial protocol, the decision on whether to complete phase III enrolment (N=700) or stop at phase II enrolment (N=400) was dependent on the recommendation by the independent Data Monitoring Committee following an interim analysis of PFS. The trial investigators and sponsor were unaware of the interim analysis results. As the pre-specified PFS hazard ratio (HR) threshold of ≤0.8 was met, the recommendation was made to progress from a phase II trial to a phase III trial.

The first patient was enrolled in April 2018. Enrolment was paused for the interim analysis in February 2019 and recommenced in September 2019. In December 2020, the last patient enrolled was randomised to treatment. Although the final OS analysis has been conducted and presented (see Section 3.4), patient follow-up is still ongoing (see Section 3.3.3). The company noted (CS, Section B.2.11) that: "The estimated trial completion date is December 2025."

Key trial eligibility criteria were the same for both phases of the trial and included the following (see CS, Appendix N for full criteria):

- patients aged ≥12 years
- histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the 8th edition of the American Joint Committee on Cancer (AJCC) staging system[50] i.e., advanced stage disease
- no prior systemic anti-cancer therapy for unresectable or metastatic melanoma (but prior adjuvant or neoadjuvant melanoma therapy with specified regimens was allowed)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (or a Lansky performance score ≥ 80% for adolescents).

Overall, patients from 114 sites in 25 countries, including [redacted] patients from the UK (clinical study report) [CSR], Section 5.3.1, Table 5.3.1-1), were randomised (1:1 ratio) to receive nivolumab-relatlimab (480mg nivolumab and 160mg relatlimab) or nivolumab (480mg) Q4W as 60-minute IV infusions until disease progression, unacceptable toxicity, withdrawal of consent, or end of the trial. No dose reductions or escalations were permitted for either treatment arm. However, patients were permitted to stop treatment for AEs and then continue treatment once AEs had resolved. Treatment beyond disease progression was permitted if the investigators assessed

that the patient was receiving clinical benefit and did not experience unacceptable treatment side effects. Clinical advice to the EAG is that patients do receive treatment beyond progression in NHS clinical practice if the patient continues to have clinical benefit.

The primary trial outcome was PFS, as assessed by BICR using RECIST (Response Evaluation Criteria in Solid Tumours) v1.1.[51] Secondary outcomes included those specified in the final scope issued by NICE. More information about outcomes is presented in Section 3.3.5, Table 9. Clinical effectiveness results from the RELATIVITY-047 trial have been reported for data cuts off dates 9 March 2021 (primary analysis), 28 October 2021 and 27 October 2022 (see also Section 3.3.2, Table 5). The data presented in the CS are largely from the latest data-cut.

3.3.2 Characteristics of RELATIVITY-047 trial patients

The company considered (CS, Sections B.2.3.3 and B.2.12.1.1) that, overall, patient characteristics were well balanced between treatment arms. However, there was a higher proportion of patients in the nivolumab-relatlimab arm (42.5%) with metastasis stage M1c (i.e., disease spread to any visceral organ and/or increased lactate dehydrogenase levels in the serum, indicating aggressive tumour growth) than in the nivolumab arm (35.4%). Also, a higher proportion of patients had metastatic sites with ≥3 lesions in the nivolumab-relatlimab arm (31.5%) than in the nivolumab arm (24.2%), and a smaller proportion of patients had only one lesion in the nivolumab-relatlimab arm (35.8%) than in the nivolumab arm (44.0%) (CS, Table 10).

Clinical advice to the company (CS, Sections B.2.3.3 and B.2.12.1.1) and to the EAG is that the RELATIVITY-047 trial population is representative of patients with previously untreated metastatic or unresectable melanoma for whom IO combination therapy is suitable in NHS clinical practice.

3.3.3 Study drug exposure and subsequent treatment received

Information about trial follow-up and drug exposure at the time of the most recent (27 October 2022) data-cut is presented in Table 6. The main differences between the treatment arms were a [redacted] proportion of patients discontinued treatment due to disease progression in the nivolumab-relatlimab arm ([redacted]) than in the nivolumab arm ([redacted]) and a [redacted] proportion discontinued treatment due to toxicity in the nivolumab-relatlimab arm ([redacted]) than in the nivolumab arm ([redacted]). Median (95% CI) time to treatment discontinuation was also [redacted] in the nivolumab-relatlimab arm ([redacted] months) than in the nivolumab arm ([redacted] months).

Table 6 Study drug exposure: updated analysis (data cut-off date 27 October 2022)

Study drug exposure	Nivolumab-relatlimab (N=355)	Nivolumab (N=359)
Patients still participating in the trial, n (%)	[redacted]	[redacted]
Patients discontinuing from trial due to death, n (%)	[redacted]	[redacted]
Patients still receiving allocated treatment, n (%)	[redacted]	[redacted]
Main reasons for discontinuing treatment		
Disease progression, n (%)	[redacted]	[redacted]
Study drug toxicity, n (%)	[redacted]	[redacted]
Median (95% CI) time to treatment discontinuation, months	[redacted]	[redacted]

[a] Range not reported
CI=confidence interval
Source: CS, Sections B.2.4.3 and B.2.10.1.1

As shown in Table 7, a [redacted] proportion of patients remained on their allocated treatment beyond progression in the nivolumab-relatlimab arm ([redacted]) than in the nivolumab arm ([redacted]). The number of patients who received a subsequent therapy (including any systemic or any IO therapy) after treatment discontinuation was similar in both arms ([redacted]).

Table 7 Treatment beyond progression and additional subsequent treatment: updated analysis (data cut-off date 27 October 2022)

Subsequent treatment received, n (%)	Nivolumab-relatlimab (N=355)	Nivolumab (N=359)
Patients receiving allocated study drug beyond progression	[redacted]	[redacted]
Patients receiving subsequent therapy	[redacted]	[redacted]
Systemic therapy	[redacted]	[redacted]
IO therapy: CTLA-4 and/or PD-L1 inhibitors	[redacted]	[redacted]
Ipilimumab monotherapy	[redacted]	[redacted]
Nivolumab+ipilimumab	[redacted]	[redacted]
Nivolumab monotherapy	[redacted]	[redacted]
Pembrolizumab monotherapy	[redacted]	[redacted]
Avelumab monotherapy	[redacted]	[redacted]

CTLA-4=cytotoxic T-lymphocyte–associated antigen 4; IO=immuno-oncology; PD-L1=programmed death ligand-1
Source: Adapted from CS, Table 16 and Clarification Question A2

Clinical advice to the EAG is that in NHS clinical practice, patients who had received a PD-L1 inhibitor in the first-line setting would not receive a PD-L1 inhibitor in the second-line setting (i.e., nivolumab or pembrolizumab) and that ipilimumab monotherapy (a cytotoxic T-lymphocyte–associated antigen 4 inhibitor) would, therefore, be the only IO therapy offered. In the RELATIVITY-047 trial, the proportion of patients receiving ipilimumab monotherapy as a subsequent treatment was [redacted] ([redacted]; a [redacted] proportion of patients received nivolumab+ipilimumab ([redacted]).

3.3.4 Quality assessment of the RELATIVITY-047 trial

The company assessed the quality of the RELATIVITY-047 trial using the Cochrane Collaboration's Risk of Bias tool[52] (CS, Appendix D.3). The company's assessments and EAG comments are presented in Table 8. The EAG considers that the RELATIVITY-047 trial was of good methodological quality and has a low risk of bias.

Table 8 Risk of bias assessment of the RELATIVITY-047 trial

Risk of bias assessment item	Company	EAG	EAG comment
Randomisation sequence generation	Unclear	Low	Stratified permuted block randomisation (TSAP, Section 2.2)
Allocation concealment	Unclear	Low	IRT system used (TSAP, Section 2.2)
Blinding of participants and personnel	Low	Low	The company, patients, investigators and site staff were blinded to the study drug administered (TSAP, Section 2.3)
Blinding of outcome assessment	Low	Low	The PFS (primary endpoint), and ORR, were assessed by BICR. OS is an objective measure and therefore is not subject to bias. The safety endpoints may have been subject to investigator and/or evaluation bias
Incomplete outcomes data	Low	Low	The company performed an ITT analysis for all efficacy and safety outcomes (CS, Section 2.6 and Appendix N, Section 2). The company provided definitions for the RELATIVITY-047 trial analysis sets in the CS (Table 11)
Selective reporting	Low	Low	The company provided results for all primary, secondary and exploratory efficacy endpoints listed in the CS (Appendix N, Table 50)
Other sources of bias	Unclear	Low	No other sources of bias were identified

BICR=blinded independent central review; EAG=External Assessment Group; IRT=interactive response technology; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TSAP=trial statistical analysis plan
Source: CS, Appendix D.3, Table 4

3.3.5 Statistical approach adopted for the analysis of the RELATIVITY-047 trial

Information relevant to the statistical approach taken by the company to analyse RELATIVITY-047 trial data relevant to the final scope issued by NICE has been extracted from the CS, the trial protocol, the primary CSR, CSR Addendum 02 and the trial statistical analysis plan (TSAP) for the CSR (see Section 3.2.1, Table 5 for references). A summary and critique of the EAG checks of the pre-planned statistical approaches used by the company to analyse data from the RELATIVITY-047 trial are provided in Table 9.

Table 9 EAG summary and critique of statistical approaches used to analyse RELATIVITY-047 trial data

Item	EAG assessment	Statistical approach	EAG comments
Were all analysis populations clearly defined & pre-specified?	Yes	Analyses of BICR-assessed PFS, investigator-assessed PFS, OS, ORR and PFS2 were carried out using data from the ITT population (all randomised patients; CS, Table 11)	The EAG is satisfied that the RELATIVITY-047 trial analysis populations were clearly defined and pre-specified in the TSAP (Section 6.3)
Was an appropriate sample size calculation and study design pre-specified?	Yes	RELATIVITY-047 trial sample size and power calculations were outlined (CS, Table 12) and were pre-specified (TSAP, Section 5). A hierarchical approach to statistical testing of the primary endpoint (BICR-assessed PFS) and secondary endpoints (OS and ORR) was also pre-specified (TSAP, Section 5). Results of an updated analysis of efficacy and safety outcomes (data cut-off date 27 October 2022) were presented in the CS. This updated analysis is not part of the hierarchical approach to statistical testing and has been performed after the final analyses of BICR-assessed PFS, OS and ORR	The EAG is satisfied that the RELATIVITY-047 trial pre-specified sample size calculation, statistical power calculations and hierarchical approach to statistical testing are appropriate and were correctly implemented. The EAG is also satisfied that clinical effectiveness results presented in the CS are appropriately interpreted with respect to the hierarchical approach. As the overall alpha of 0.05 was spent at the final OS analysis (data cut-off date 28 October 2021), all updated analyses presented in the CS are descriptive only (CSR Addendum 02, Section 1) and statistical significance should not be inferred from these results
Were all changes in the conduct of the study or planned analysis made prior to analysis?	Yes	Changes in the conduct of the study or planned analyses and the rationale for amendments to the protocol were listed in the primary CSR (Section 4.1 and Section 4.2) and in the document history of the TSAP (Section 10). Latest versions of the protocol (Amendment 3, version 8.0, date 23 November 2020) and the TSAP (version 6.0, date 25 May 2022) were finalised prior to the data cut-off date of the updated efficacy and safety analyses presented in the CS (27 October 2022)	The EAG considers that all changes to the protocol and TSAP were reasonable, justified, and made prior to the data cut-off dates of the updated analyses presented in the CS

Item	EAG assessment	Statistical approach	EAG comments
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary, secondary and exploratory efficacy endpoints presented in the CS were listed in CS, Appendix N, Table 50. Endpoint definitions and analysis approaches were pre-specified in the TSAP (Section 7.5). The company analysed PFS outcomes and OS using Cox PH models. This analysis approach requires the assumption of PH, i.e., the event hazards associated with the intervention and comparator data are proportional over time. The company assessed the PH assumption by plotting the log cumulative hazard versus log(time), by plotting Schoenfeld residuals versus time and by using the Grambsch-Therneau test[53] of PH (CS, Appendix D 4.1.2 and Appendix O.2). Based on these assessments, the company considered that there is uncertainty whether the PH assumption holds (CS, Section B.2.9.1.1.2). However, there may be evidence that the PH assumption does not hold for BICR-assessed PFS (CS, Appendix O.2.2.1) and for OS (CS, Appendix O.2.1.1)	The EAG agrees with the company that there is uncertainty around whether the PH assumption holds for BICR-assessed PFS and OS from visual inspection of the Schoenfeld Residuals plots and the log cumulative hazards plots. The EAG notes that the observed deviations of Schoenfeld Residuals plots from a zero slope and of log cumulative hazard plots from parallel survival curves may indicate violation of the PH assumption. However, such deviations, as well as divergence of K-M curves may also reflect large numbers of censored participants, particularly after 30 months. Furthermore, the Grambsch-Therneau test[53] of PH is not statistically significant for BICR-assessed PFS nor for OS. Therefore, the EAG considers that the HR is a suitable measure of relative treatment effect for BICR-assessed PFS and OS over the observed RELATIVITY-047 trial period. The company did not provide assessments of investigator-assessed PFS or PFS2, therefore it is unknown whether the PH assumption holds for these outcomes
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs presented in the CS (Appendix N.2.2) and clarification response (Clarification Question A7) were change from baseline in the FACT-M sum score and subscale scores, the EQ-5D-3L utility index score and the EQ-5D-3L VAS score assessed in all patients who have completed the FACT-M or EQ-5D-3L questionnaire at baseline and at ≥1visit post baseline. PROs were analysed using an MMRM approach. The analyses of PROs were considered exploratory	The EAG is satisfied that the analysis approaches were appropriate and pre-specified in the TSAP (Section 4.3.4 and Section 7.9). Additional analyses of RELATIVITY-047 trial PRO data (TTSD) are provided in the CSR
Was the analysis approach for AEs appropriate and pre-specified?	Yes	AEs were assessed and graded using the NCI CTCAE version 5.0 classification system within the treated population (all randomised patients who received at least one dose of study medication [Protocol, Section 10.2.3]). AEs were presented as numbers and percentages of patients experiencing events by treatment arm and by CTCAE grade (Any Grade and Grade 3 to 4). No formal statistical analyses of AEs were conducted. An overview of AEs, TRAEs, SAEs, TRSAEs, AEs and TRAEs leading to study drug discontinuation, frequently reported TRAEs, immune mediated AEs and deaths were presented in the CS (Section B.2.10.1)	The EAG is satisfied that the analysis approach for AEs was pre-specified (TSAP, Section 7.6) and is appropriate. Additional summary tables of RELATIVITY-047 trial safety data were provided in the CSR Addendum 02 (Section 8)

Item	EAG assessment	Statistical approach	EAG comments
Was a suitable approach used for handling missing data?	Yes	The company's approach to handling missing data and censored data (PFS and OS) were outlined in the CS (Table 12 and Appendix N.1.2)	The EAG is satisfied that the approach described was appropriate and was pre-specified in the TSAP (Section 4.1.1 and Section 8)
Were all subgroup and sensitivity analyses pre-specified?	Yes	Subgroup analyses of BICR-assessed PFS OS and ORR in the ITT population by stratification factors used in the RELATIVITY-047 trial were presented in the CS (Section B2.7; tumour PD-L1 expression (≥1% vs <1%), LAG-3 expression (≥1% vs <1%), *BRAF* mutation (V600 mutation positive vs V600 wild-type) and AJCC v8 metastatic stage (M0 or M1 with normal LDH levels vs M1 with elevated LDH levels) Further pre-specified subgroup analyses of BICR-assessed PFS, OS and ORR in the ITT population were presented in CS, Appendix E. No sensitivity analyses were presented in the CS	The EAG is satisfied that all subgroup analyses presented in the CS were pre-specified in the TSAP (Section 7.5.3)

AE=adverse event; AJCC=American Joint Committee on Cancer; BICR=blinded independent central review; CS=company submission; CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; EAG=External Assessment Group; EQ-5D-3L=European Quality of Life 5 Dimensions 3 Level Version; FACT-M=Functional Assessment of Cancer Therapy-Melanoma; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; LAG-3=lymphocyte activation gene-3; LDH=lactate dehydrogenase; MMRM=mixed model for repeated measures; NCI=National Cancer Institute; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PFS2=progression-free survival on next line of therapy; PH=proportional hazards; PRO=patient-reported outcome; SAE=serious adverse event; TRAE=treatment-related adverse event; TRSAE=treatment-related serious adverse event; TSAP=trial statistical analysis plan; TTSD=time to meaningful symptomatic deterioration
Source: CS, primary CSR[33] and CSR Addendum 02,[34] TSAP[35] and trial protocol[32]

3.4 *RELATIVITY-047 trial efficacy results*

This section includes intention-to-treat (ITT) population clinical effectiveness results from the RELATIVITY-047 trial (data cut-off date 27 October 2022). The median follow-up duration for this data cut-off date was [redacted] months (range: [redacted] to [redacted] months; [redacted] months in the nivolumab-relatlimab arm and [redacted] months in the nivolumab arm).

Due to the hierarchical approach to statistical testing used, the overall alpha of 0.05 was spent in the OS final analysis (data cut-off date 28 October 2021). Therefore, all updated analysis results are descriptive, no p-values are presented and statistical significance should not be inferred from these results.

3.4.1 Progression-free survival

BICR-assessed and investigator-assessed PFS results are presented in Table 10.

Table 10 RELATIVITY-047 trial ITT population PFS results: updated analysis (data cut-off date 27 October 2022)

Outcome measure	Nivolumab-relatlimab (N=355)	Nivolumab (N=359)
BICR-assessed PFS		
Events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Median PFS (95% CI),[a] months	[redacted]	[redacted]
HR (95% CI)[b,c]	[redacted]	
Investigator-assessed PFS		
Events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Median PFS (95% CI),[a] months	[redacted]	[redacted]
HR (95% CI)[b,c]	[redacted]	

[a] Calculated from Kaplan-Meier estimates
[b] Calculated from Cox proportional hazards model stratified by tumour PD-L1 expression (≥ 1% vs < 1%), LAG-3 expression (≥ 1% vs < 1%), *BRAF* mutation (V600 mutation positive vs V600 wild-type) and AJCC v8 metastatic stage (M0 or M1 with normal LDH levels vs M1 with elevated LDH levels). HR<1 indicates an advantage to nivolumab-relatlimab over nivolumab and assumes proportional hazards
[c] Due to the hierarchical approach to statistical testing used, the overall alpha of 0.05 was spent in the OS final analysis (data cut-off date 28 October 2021). Therefore, all updated analysis results are descriptive, no p-values are presented and statistical significance should not be inferred from these results.
AJCC=American Joint Committee on Cancer; BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; LAG-3=lymphocyte activation gene-3; LDH=lactate dehydrogenase; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival
Source CS, Table 13, CSR Addendum 02[34] and Clarification Question A5

The RELATIVITY-047 trial primary outcome was BICR-assessed PFS; investigator-assessed PFS was an exploratory outcome.[32] The EAG agrees with the company that the use of BICR for the objective assessment of radiological outcomes can reduce the risk of systematic investigator bias which may favour one treatment arm (Clarification Question A5); however, the EAG considers that the risk of investigator bias should be reduced in double-blinded trials such as the RELATIVITY-047 trial.[54]

Median BICR-assessed PFS was longer in the nivolumab-relatlimab arm ([redacted]) than in the nivolumab arm ([redacted]; [redacted]). Median investigator-assessed PFS was also longer in the nivolumab-relatlimab arm ([redacted]) than in the nivolumab arm ([redacted]); however, [redacted]The company provided concordance values between BICR-assessed and investigator-assessed PFS from the October 2021 data cut-off of the RELATIVITY-047 trial (Clarification Question A5, Table 1 and Table 2). For patients in the nivolumab arm, [redacted] PFS events were observed for investigator-assessed PFS (n=[redacted]) than for BICR-assessed PFS (n=[redacted]) and for patients in the nivolumab-relatlimab arm, [redacted] PFS events were observed for BICR-assessed PFS (n=[redacted]) than for investigator-assessed PFS (n=[redacted]). This pattern in the number of BICR-assessed and investigator-assessed PFS events was [redacted] observed for the most recent October 2022 data cut-off of the RELATIVITY-047 trial (Table 10). At the October 2021 data-cut, median BICR-assessed and investigator-assessed PFS were similar for nivolumab-relatlimab ([redacted] versus [redacted], respectively), median investigator-assessed PFS was longer ([redacted]) for nivolumab than BICR-assessed median PFS ([redacted]).

The company considered that investigator-assessed PFS was biased [redacted] and that BICR-assessed PFS should be utilised (see Clarification Question A5 for further details). However, the EAG notes that concordance between the number of BICR-assessed and investigator-assessed PFS events was actually higher in the nivolumab arm ([redacted]) than in the nivolumab-relatlimab arm ([redacted]) at the October 2021 data cut (the company did not provide concordance values for the October 2022 data-cut).

Regarding the external validity of the data, the EMA CHMP[7] (p108) noted that median PFS in the nivolumab arm of the RELATIVITY-047 trial was “somewhat lower than expected” based on CheckMate 067 trial[17] results. However, the EMA CHMP highlighted that median BICR-assessed PFS was reported from the RELATIVITY-047 trial while median investigator-assessed PFS was reported from the CheckMate 067 trial.[17] Median investigator-assessed PFS for the nivolumab arm in the two trials was [redacted] (RELATIVITY-047 trial: [redacted] months; CheckMate 067 trial:[17] 6.9 months).

3.4.2 Overall survival

The RELATIVITY-047 trial ITT population OS results are based on immature data, as presented in Table 11.

Table 11 RELATIVITY-047 trial ITT population OS results: updated analysis (data cut-off date 27 October 2022)

Outcome measure	Nivolumab-relatlimab (N=355)	Nivolumab (N=359)
Deaths, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Median OS (95% CI),[a] months	[redacted]	[redacted]
HR (95% CI)[b,c]	[redacted]	

[a] Calculated from Kaplan-Meier estimates
[b] Calculated from Cox proportional hazards model stratified by tumour PD-L1 expression (≥ 1% versus < 1%), LAG-3 expression (≥ 1% versus < 1%), *BRAF* mutation (V600 mutation positive versus V600 wild-type) and AJCC v8 metastatic stage (M0 or M1 with normal LDH levels versus M1 with elevated LDH levels). HR<1 indicates an advantage to nivolumab-relatlimab over nivolumab and assumes proportional hazards
[c] Due to the hierarchical approach to statistical testing used, the overall alpha of 0.05 was spent in the OS final analysis (data cut-off date 28 October 2021). Therefore, all updated analysis results are descriptive, no p-values are presented and statistical significance should not be inferred from these results
AJCC=American Joint Committee on Cancer; CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; LAG-3=lymphocyte activation gene-3; LDH=lactate dehydrogenase; NR=not reached; OS=overall survival; PD-L1=programmed cell death-ligand 1
Source: CS, Table 14 and CSR Addendum 02[34]

Regarding the external validity of the data, median OS in the nivolumab arms of the RELATIVITY-047 trial ([redacted] months) and CheckMate 067 trial[17] are similar (36.9 months [after 7.5 years follow-up]).

3.4.3 Objective response rate and duration of response

BICR-assessed ORR was higher in the nivolumab-relatlimab arm than in the nivolumab arm ([redacted] versus [redacted]; odds ratio=[redacted]). The difference in BICR-assessed ORR between nivolumab-relatlimab and nivolumab [redacted] ([redacted]). The median duration of response in responders was "[redacted]" for both treatment arms (CS, p44). ITT population BICR-assessed ORR results are presented in Table 12.

The external validity of the ORR data cannot be assessed as ORR was BICR-assessed in the RELATIVITY-047 trial and was investigator-assessed in the CheckMate 067 trial.[17]

Table 12 RELATIVITY-047 trial ITT population BICR-assessed ORR results: updated analysis (data cut-off date 27 October 2022)

	Nivolumab-relatlimab (N=355)	Nivolumab (N=359)
ORR (CR+PR), n (%)	[redacted]	[redacted]
CR, n (%)	[redacted]	[redacted]
PR, n (%)	[redacted]	[redacted]
95% CI for ORR[a]	[redacted]	[redacted]
Difference of ORR, % (95% CI)[b]	[redacted]	
Odds ratio (95% CI)[b,c]	[redacted]	

[a] CI based on the Clopper and Pearson method
[b] Difference of ORR and odds ratio calculated using Cochran-Mantel-Haenszel test stratified by tumour PD-L1 expression (≥ 1% versus < 1%), LAG-3 expression (≥ 1% versus < 1%), BRAF mutation (V600 mutation positive versus V600 wild-type) and AJCC v8 metastatic stage (M0 or M1 with normal LDH levels versus M1 with elevated LDH levels). Difference of ORR>0 and OR<1 indicates an advantage to nivolumab-relatlimab over nivolumab
[c] Due to the hierarchical approach to statistical testing used, the overall alpha of 0.05 was spent in the OS final analysis (data cut-off date 28 October 2021). Therefore, all updated analysis results are descriptive, no p-values are presented and statistical significance should not be inferred from these results
AJCC=American Joint Committee on Cancer; BICR=Blinded Independent Central Review; CI=confidence interval; CR=complete response; HR=hazard ratio; ITT=intention-to-treat; LAG-3=lymphocyte activation gene-3; LDH=lactate dehydrogenase; OR=odds ratio; ORR=objective response rate; PD-L1=programmed cell death-ligand 1; PR=partial response
Source: CS, Table 15 and CSR Addendum 02[34]

3.4.4 Progression-free survival after the next line of therapy

As presented in Section 3.3.3 of this EAG report, [redacted] of patients in the nivolumab-relatlimab arm and [redacted] of patients in the nivolumab arm received subsequent therapy during the RELATIVITY-047 trial. Progression-free survival after the next line of therapy (PFS2) per investigator assessment, defined as the time from randomisation to documented progression after the next line of therapy, or to death from any cause, whichever occurred first, was reported as an exploratory outcome.

PFS2 per investigator assessment was longer in the nivolumab-relatlimab arm than in the nivolumab arm (median PFS2 [redacted] versus [redacted], respectively; [redacted]).

3.4.5 Subgroup analyses

Subgroup analyses were presented for BICR-assessed PFS, OS and ORR.

PFS subgroup analyses results (CS, Figure 6; Appendix E, Figure 8) suggested at least a numerical advantage in BICR-assessed PFS for patients treated with nivolumab-relatlimab compared to nivolumab for most subgroups. The exceptions were patients recruited in phase III of the RELATIVITY-047 trial, patients with PD-L1 tumour expression ≥1%, ≥5% or ≥10% and for patients with both LAG-3 expression ≥1% and PD-L1 tumour expression ≥1%.

OS subgroup analyses results (CS, Figure 6; Appendix E, Figure 8) suggested at least a numerical advantage for patients treated with nivolumab-relatlimab compared to nivolumab for most subgroups. The exceptions were patients recruited in phase III of the RELATIVITY-

047 trial, patients recruited in Latin America, patients with baseline metastasis stage M1a, patients with cutaneous acral or mucosal histology, patients with ECOG PS of 1 at baseline and patients with PD-L1 tumour expression ≥10%.

ORR subgroup analysis results (CS, Appendix E, Figure 9) suggested at least a numerical advantage for patients treated with nivolumab-relatlimab compared to nivolumab for most subgroups. The exceptions were [redacted].

For all subgroup analyses, the EAG considers that the imprecise comparative results, reflected by wide 95% CIs (due to small sample sizes and low event counts), and the imbalanced subgroup sizes should be considered when interpreting subgroup results.

The EAG notes that the EMA CHMP[7] used the results from subgroup analyses for PD-L1 tumour expression to inform its decision when granting the marketing authorisation for nivolumab-relatlimab for use in the European Union. The EMA only licensed treatment with nivolumab-relatlimab for patients "with tumour cell PD-L1 expression < 1%"[7] because the EMA CHMP[7] (p141) considered that evidence from the RELATIVITY-047 trial showed "little additional [PFS or OS] benefit" for nivolumab-relatlimab versus nivolumab for patients with PD-L1 tumour expression ≥1%. The EAG notes that the EMA CHMP's[7] decision was based on results from the 28 October 2021 data-cut. The results from the latest data cut (27 October 2022) were [redacted] to those from the 28 October 2021 data cut (Table 13).

The EAG highlights that in both the nivolumab-relatlimab and nivolumab arms of the RELATIVITY-047 trial, median BICR-assessed PFS was [redacted] for patients with PD-L1 tumour expression <1% ([redacted] months and [redacted] months, respectively) than for the ITT population ([redacted] months and [redacted] months, respectively); a greater relative treatment effect (as expressed by HRs) was also found for BICR-assessed PFS in patients with PD-L1 tumour expression <1% than in the ITT population ([redacted] and [redacted], respectively).

Table 13 Subgroup analysis results for PD-L1 expression (<1%, ≥1%): (data cut-off date 28 October 2021 and 27 October 2022)

Outcome	Data cut-off date 28 October 2021				Data cut-off date 27 October 2022			
	PD-L1<1%		PD-L1≥1%		PD-L1<1%		PD-L1≥1%	
	Nivolumab-relatlimab (N=209)	Nivolumab (N=212)	Nivolumab-relatlimab (N=146)	Nivolumab (N=147)	Nivolumab-relatlimab (N=209)	Nivolumab (N=212)	Nivolumab-relatlimab (N=146)	Nivolumab (N=147)
Progression-free survival per blinded independent central review								
HR (95% CI)[a]	0.68 (0.53 to 0.86)		0.96 (0.70 to 1.30)					
Events, n	124	155	80	78				
Median, months (95% CI)	6.67 (4.67 to 11.99)	2.96 (2.79 to 4.50)	15.74 (10.12 to 28.45)	14.72 (5.36 to 22.97)				
Overall survival								
HR (95% CI)[a]	0.78 (0.59 to 1.04)		0.84 (0.57 to 1.24)					
Events, n	89	104	48	56				
Median, months (95% CI)	NE (27.43 to NE)	27.04 (17.12 to NE)	NE (NE to NE)	NE (31.97 to NE)				
Objective response rate (ORR) per blinded independent central review								
ORR difference[a,b] (95% CI)	Not reported[c]		Not reported[c]					
Events, n (%)	76 (36.4)	51 (24.1)	77 (52.7)	66 (44.9)				
95% CI for ORR	29.8 to 43.3	18.5 to 30.4	44.3 to 61.1	36.7 to 53.3				

[a] Due to the hierarchical approach to statistical testing used, the overall alpha of 0.05 was spent in the OS final analysis (data cut-off date 28 October 2021). Therefore, all updated analysis results are descriptive, no p-values are presented and statistical significance should not be inferred from these results
[b] Unweighted ORR
[c] It is reported in the EMA EPAR[7] (p90) that "An ORR difference of ~8% to 12% was observed" for nivolumab-relatlimab vs nivolumab "across the majority of PD-L1 expression levels"
CI=confidence interval; HR=hazard ratio; NE=not estimable; PD-L1=programmed cell death-ligand 1
Source: EMA EPAR, [7] Table 26 and Figure 19; CS, Appendix E, Figure 11 and Figure 12; CSR Addendum 02, Table 7.5.2-1

3.5 *Patient reported outcomes from the RELATIVITY-047 trial*

Exploratory patient reported outcome (PRO) data were derived from the data-cut for the primary analysis of PFS (9 March 2021). The summary and interpretation of results are presented in Sections 3.5.1 to 3.5.3.

3.5.1 HRQoL data reported in the CS

As reported in the CS (Appendix N.2.2) and in Schadendorf 2021,[36] HRQoL data were collected at baseline and prior to dosing in each 4-week treatment cycle. Results for a timepoint were only reported when the number of available PRO assessments for each treatment arm was ≥10. Results were available every 4 weeks up until Week 120 (CS, Appendix N, Figures 26 to 32). Clinically meaningful changes from baseline were determined using pre-specified minimally important differences (MIDs).

All HRQoL results from the RELATIVITY-047 trial were considered exploratory and were reported for the ITT population using data for the following outcomes (CS, Appendix N, Figures 26 to 32; Schadendorf 2021,[36] Figures 1 to 4):

- change from baseline of Functional Assessment of Cancer Therapy-melanoma (FACT-M) total, FACT-M trial outcome index (TOI) and FACT-general (FACT-G) total scores
- change from baseline of FACT-M melanoma subscale
- change from baseline of FACT-G subscale scores for physical well-being and functional well-being
- FACT-M physical well-being module question 5 from the Functional Assessment of Chronic Illness Therapy item GP5 (FACIT GP5): 'I am bothered by side effects of treatment' (at 12-weekly intervals)
- change from baseline of European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L) utility index and visual analogue score.

Additional HRQoL data collected from patients on treatment but only reported in the CSR (not the CS or Schadendorf 2021[36]) were [redacted]

According to the trial protocol, HRQoL data were also collected off treatment at follow-up visits (first visit: 30 [±7] days from last dose or, if >42 days since last dose, date of discontinuation [±7 days]; second visit: 100 [±7] days) and survival follow-up visits (first visit: 3 months [±14 days] after second follow-up visit, subsequent survival follow-up visits every 3 months [±14 days]). EQ-5D-3L data were collected at all follow-up and survival follow-up visits, FACT-M

data at the two follow-ups and FACT-M MS data at the survival follow-up visits. The company provided off-treatment EQ-5D-3L but not FACT-M or FACT-M MS data at clarification (Clarification Question A8).

3.5.2 Summary and interpretation of reported HRQoL results: on-treatment

On-treatment questionnaire completion rates were ≥86% at each treatment visit (CS, Appendix N.2.2). HRQoL scores were relatively stable over time, i.e., close to baseline values at each time point with differences in least squares mean from baseline not exceeding MID (with the exception of EQ-5D-3L utility index in the nivolumab-relatlimab arm at Week 108). The company therefore considered there were no notable differences between the two treatment arms. The EAG agrees with this interpretation of the results [redacted]

In relation to FACIT GP5 results (CS, Appendix N.2.2, Figure 32) at Weeks 36, 48, 72, 84, 96 and 108:

- a higher proportion (≥10% difference) of patients in the nivolumab arm reported being 'not at all bothered by side effects of treatment' than in the nivolumab-relatlimab arm and
- a higher proportion (≥10% difference) of patients in the nivolumab-relatlimab arm reported being 'a little bit' or 'somewhat' bothered by side effects of treatment than in the nivolumab arm.

As a higher proportion of patients experienced TRAEs in the nivolumab-relatlimab arm than in the nivolumab arm (see Section 3.6), the FACIT GP5 results were expected. The proportions of patients reporting being bothered 'quite a bit' or 'very much' by TRAEs were relatively low at all time points (always ≤5% at the 12-weekly intervals shown) "suggesting a perceived treatment tolerance with nivolumab-relatlimab" (CS, Appendix N.2.2, p264).

3.5.3 Summary and interpretation of reported HRQoL results: off-treatment

The HRQoL results for patients off-treatment (Clarification Question A8) showed that:

- time off-treatment questionnaire completion rates were much lower [redacted] than time on-treatment questionnaire completion (≥86%)
- summary statistics for EQ-5D-3L utilities using the Dolan 1997 value set for the UK[55] showed that mean (standard deviation) utility scores were similar in both arms: nivolumab-relatlimab [redacted] ([redacted]) versus nivolumab [redacted] ([redacted]) (Clarification Question A8, Table 10)

- summary statistics provided across all visits, by treatment arm and by treatment status (on-treatment versus off-treatment) showed that patients on treatment had a higher utility ([redacted]) compared to patients off treatment ([redacted]); this was true in both arms of the trial (nivolumab-relatlimab [redacted] versus [redacted], nivolumab [redacted] versus [redacted]; Clarification Question A8, Table 10).

The EAG considers off-treatment HRQoL data are informative since clinical advice to the EAG is that IO therapy may have an ongoing effect on efficacy and safety (and therefore HRQoL) after cessation of treatment. The EAG highlights that off-treatment PROs will also be affected by any subsequent treatment(s) received but, as the use of subsequent treatments was similar in both treatment arms (see Section 3.3.3), this should not result in bias. However, the low questionnaire completion rates for patients off-treatment may affect the representativeness of the results.

3.6 *Safety and tolerability results from the RELATIVITY-047 trial*

Safety data reported in the CS were from the most recent (27 October 2022) data-cut. Similar AEs were reported in both treatment arms but the frequency and severity for some AEs differed (Sections 3.6.1 to Section 3.6.5).

3.6.1 Total adverse events

Nearly all patients in either treatment arm experienced an AE (Table 14). The numbers of patients experiencing any grade TRAEs or Grade 3 to 4 TRAEs were notably higher ([redacted]) in the nivolumab-relatlimab arm than in the nivolumab arm. Incidences of serious AEs (SAEs; any causality or treatment-related) were also higher in the nivolumab-relatlimab arm than in the nivolumab arm. The company reported (CSR Addendum 02, Section 8.3) that [redacted] patients in the nivolumab-relatlimab arm and [redacted] patients in the nivolumab arm experienced treatment-related deaths (CS, Section B.2.10.1.4).

Table 14 Summary of RELATIVITY-047 trial adverse events (ITT population; data cut-off date 27 October 2022)

Adverse events	Nivolumab-relatlimab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
Any AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TRSAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; ITT=intention-to-treat; SAE=serious adverse event; TRAE=treatment-related adverse event; TRSAE=treatment-related serious adverse event
Source: Clarification question C3, Table 34 (corrected version of CS, Table 19)

3.6.2 Treatment-related adverse events

The most frequent types of TRAEs experienced by RELATIVITY-047 trial patients were similar for patients in the nivolumab-relatlimab and nivolumab arms (Table 14). For any grade TRAEs, the difference in frequency was [redacted] between arms for pruritis, fatigue, diarrhoea, arthralgia (Table 15) and increased aspartate transaminase (AST) ([redacted] versus [redacted]). [redacted]

Table 15 Summary of very common* RELATIVITY-047 trial treatment-related adverse events (ITT population; data cut-off date 27 October 2022)

Adverse events	Nivolumab-relatlimab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3 to 4	Any grade	Grade 3 to 4
Pruritus, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rash, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Vitiligo, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

* Very common defined as frequency [redacted] in either treatment arm
ITT=intention-to-treat
Source: CS, Table 20

3.6.3 Immune-mediated adverse events

The most frequent types of reported immune-mediated AEs (IMAEs) were similar for patients in the nivolumab-relatlimab and nivolumab arms (CS, Table 21). All of these IMAEs (except for hyperthyroidism) were more frequent in the nivolumab-relatlimab arm than in the nivolumab arm, but the between arm difference in frequencies was never [redacted]. Very common ([redacted]) IMAEs were: hypothyroidism/thyroiditis (nivolumab-relatlimab: [redacted]; nivolumab: [redacted]), hypothyroidism (nivolumab-relatlimab: [redacted]; nivolumab: [redacted]) and rash (nivolumab-relatlimab: [redacted]; nivolumab: [redacted]). The most common Grade 3 to 4 IMAE in both arms was hepatitis (nivolumab-relatlimab: [redacted]; nivolumab: [redacted]). All other Grade 3 to 4 IMAEs occurred in [redacted] of patients in either arm.

3.6.4 Other serious adverse events

A summary of the types of SAEs experienced was not presented in the CS. However, it is reported in the draft SmPC[6] (based on the October 2021 data-cut) that, for patients treated with nivolumab-relatlimab, [redacted]

3.6.5 Adverse events leading to dose delay/discontinuation

The total number and most frequent types of AEs leading to dose delay and permanent discontinuation of AEs are summarised in Table 16. The frequencies of dose delays were similar between treatment arms. The frequency of AEs leading to permanent discontinuation was [redacted] in the nivolumab-relatlimab arm than in the nivolumab arm.

Table 16 Summary of AEs resulting in temporary or permanent cessation of study drug in RELATIVITY-047 (ITT population; data cut-off date 27 October 2022)

AE impact on treatment decision	Nivolumab-relatlimab (N=355)		Nivolumab (N=359)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Dose delay				
AEs, n (%)	[redacted]	NR[a]	[redacted]	NR[a]
TRAEs, n (%)	NR[a]	NR[a]	NR[a]	NR[a]
Most common TRAEs resulting in dose delay[b]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Permanent discontinuation				
AEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
TRAEs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common TRAEs resulting in permanent discontinuation[b]				
Myocarditis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Colitis, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Data appear to be available in CSR addendum 2, Table S.6.4.2.3 and/or Table S.6.4.2.4 but these tables were not provided to the EAG; data requested during clarification but "not attainable in the short timeframe to respond to EAG clarification questions" (Clarification Question A6)
[b] frequency [redacted] (Any Grade) in either arm
AE=adverse event; ALT=alanine transaminase; AST=aspartate transaminase; ITT=intention-to-treat; NR=not reported; TRAE=treatment-related adverse event
Source: CS, Table 19, Clarification Question A6 and CSR Addendum 02,[34] Section 6.3

3.6.6 Summary and interpretation of safety and tolerability results from the RELATIVITY-047 trial

The company considered the safety profile of nivolumab-relatlimab was manageable and consistent with the known mechanisms of action of both drugs, with no new safety signals or events identified (CS, B.2.10.1.2). Clinical advice to the EAG is that the reported TRAEs and IMAEs are well known to clinicians using IO therapies and can be managed; IMAEs usually respond to treatment with corticosteroids. Clinical advice to the EAG is that while most AEs experienced by patients occur within the first year of treatment, AEs can occur at any time on-treatment, and off-treatment, and that patients are monitored for AEs long term.

3.7 *EAG critique of the indirect evidence*

In the absence of direct evidence to inform the comparisons of nivolumab-relatlimab versus nivolumab+ipilimumab and versus pembrolizumab, the company performed NMAs. The company performed NMAs to estimate both time-varying HRs (fractional polynomials [FPs]) and constant HRs. The EAG has replicated the company NMAs (where possible) and has performed some additional NMAs.

The company has also performed adjusted ITCs for the comparison of nivolumab-relatlimab versus nivolumab+ipilimumab using PLD from the RELATIVITY-047 and CheckMate trials.[17,18] This approach was adopted to adjust the nivolumab-relatlimab versus nivolumab+ipilimumab comparison for confounding which may be attributed to differences in baseline patient characteristics which are potential treatment effect modifiers.

3.7.1 Critique of trials identified and included in the NMAs and adjusted ITCs

The company conducted a SLR to identify relevant trials (see Section 3.1 for further details) for inclusion in the NMAs. The company search process identified 16 RCTs[16-31] that met the broad SLR inclusion criteria. The company excluded 12 trials[20-31] that investigated treatments that were not relevant to the decision problem (CS, Table 1). The EAG agrees that these exclusions were appropriate. The remaining four trials[16-19] included in the NMAs investigated nivolumab-relatlimab and relevant comparator treatments for adult patients with previously untreated unresectable or metastatic melanoma, independent of *BRAF* mutation and PD-L1 status (CS, Section 2.9.1). A summary of the relevant publications for each trial is presented in Section 3.2.1, Table 5.

Summaries of the included trial designs, eligibility criteria and outcome definitions were provided in the CS (Appendix D4.1.1). Key baseline patient characteristics are provided in Appendix 1 (Section 8.1, Table 59).

Trial design and baseline patient characteristics

The following differences between trials may have introduced heterogeneity into the company and EAG NMAs:

- two trials were phase III RCTs,[17,19] one was a phase II RCT[18] and one was a phase II/III RCT[16]
- three trials were double-blind trials[16-18] and one was an open-label trial[19]
- the median age of patients enrolled in the trials ranged from 60 years[17] to 67 years[18]
- the proportion of male patients in the trials ranged from 58%[16] to 67%[18]
- patients with AJCC Stage III or IV unresectable or metastatic melanoma and ECOG PS score 0 or 1 were eligible for inclusion in all trials[16-19]
    - most patients in the trials[16-19] had an ECOG PS score of 0 (67%[16] to 82%[18]), although one trial[17] enrolled one patient with an ECOG PS score of 2 and one trial[18] enrolled or two patients with an ECOG PS score of 2
    - in three trials,[16-18] most patients had Stage IV disease (ranging from 87% of patients[18] to 93% of patients[17]). In the KEYNOTE-006 trial,[19] the proportions of patients with Stage III and Stage IV disease were not reported
- the proportions of patients with each AJCC metastasis stage at baseline varied (e.g., the proportion of patients with stage M1c metastases ranged from 39%[16] to 65%[19])
- all trials excluded patients with active or untreated brain metastases, but a small proportion of the enrolled patients (3%[16,18] to 9%[19]) had a history of brain metastases
- three trials only recruited patients with previously untreated unresectable or metastatic melanoma; however, in the KEYNOTE-006 trial,[19] 34% of the patients had received one line of previous systemic therapy for advanced disease.

The company considered, and the EAG agrees, that the ITT KEYNOTE-006 trial[19] population is, in some respects, different from the populations enrolled in the other three trials.[16-18] In the KEYNOTE-006 trial,[19] approximately a third (34%) of patients had received one line of previous systemic therapy for advanced disease and a higher proportion of patients (9%) had brain metastases than in the other three trials.[16-18] All patients in the KEYNOTE-006 trial[19] were treated with IO monotherapy (i.e., pembrolizumab or ipilimumab) and therefore it is unclear whether IO combination therapy would have been suitable for these patients; however the KEYNOTE-006 trial[19] eligibility criteria were similar to the trial eligibility criteria in the other trials.[16-18] The company and the EAG have included KEYNOTE-006 trial[19] treatment naïve subgroup (i.e., those receiving first-line treatment with pembrolizumab or ipilimumab for advanced disease) outcome data in the efficacy outcome NMAs; however, safety data were only available for the KEYNOTE-006 trial[19] safety population.

Trial outcomes

The company conducted PFS and OS NMAs (estimating time-varying HRs and constant HRs), and safety outcome NMAs (Grade 3 to 4 AEs and TRAEs, discontinuation due to AEs and TRAEs). The EAG has replicated company PFS, OS and safety outcomes NMAs (constant

HRs). Outcome data included in the company and EAG NMAs are presented in Appendix 2 (Section 8.2, Table 61 and Table 62). Outcome follow-up times varied from a median of [redacted] months[34] up to a minimum of 90 months;[44] this variation may have introduced heterogeneity into the NMA analyses and results.

PFS and OS outcome definitions

All the trials[16-19] included in company and EAG NMAs:

- defined a PFS event as documented progression, or death due to any cause, whichever occurs first
- censored PFS at the latest date a patient was known to be alive without disease progression
- censored PFS at the date of the last evaluable tumour assessment prior to the initiation of subsequent anti-cancer therapy for patients who started anti-cancer therapy without a prior reported progression
- defined an OS event as death due to any cause and censored OS at the last date a patient was known to be alive.

Three trials[16,17,19] measured PFS and OS from the date of randomisation and one trial[18] measured OS from the date of first treatment. The EAG considers the difference in the PFS and OS definitions across the trials is a source of heterogeneity, although this minor difference is unlikely to impact NMA results.

Two trials[17,18] reported unblinded investigator-assessed radiologic outcomes (i.e., PFS and ORR) while the other two trials[16,19] reported BICR- and investigator-assessed radiologic outcomes. Investigator-assessed PFS data from three trials[44,45,49] and BICR-assessed PFS data from the RELATIVITY-047 trial[34] were included in the company NMAs (see Table 17 for further discussion).

EAG concluding remarks

The EAG is not aware of any statistical methods that can be used to adjust for all differences in baseline patient characteristics, trial design, outcome definitions and outcome follow-up periods. The impact of these differences on company and EAG NMA results is not known.

3.7.2 Quality assessment of the trials included in the NMAs and adjusted ITCs

The company and the EAG assessed the quality of the trials included in the NMAs and adjusted ITCs using the Cochrane Collaboration's Risk of Bias tool.[52] Company assessments were presented in the CS (Appendix D.3) and EAG assessments and comments are presented in Appendix 1 (Section 8.1, Table 60). The EAG considers that all four trials[16-19] were of good methodological quality and mostly had a low risk of bias. All trials concealed

allocation using central interactive response technologies; three trials[16-18] used stratified permuted block randomisation and the method of randomisation was not specified for one trial.[19] Three trials[16-18] blinded the sponsor, patients, investigator and site staff and in one trial[19] only outcome assessors (i.e., statistical team and independent radiologists conducting central review of progression) were blinded (i.e., the sponsor, patients and site staff were not blinded to treatment). All trials[16-19] used an ITT approach which minimised attrition bias and there is no evidence of selective reporting or other biases in any of the trials.

3.7.3 Methodological approach to the NMAs and adjusted ITCs

A summary and EAG critique of the statistical approaches used to conduct the company NMAs are provided in Table 17. A summary and EAG critique of the statistical approaches used to conduct the adjusted ITCs are provided in Table 18.

Table 17 EAG summary and critique of the company statistical approaches to NMAs

Item	EAG assessment	Summary of company approach	EAG comments
Were NMAs conducted for all relevant outcomes?	No	The company presented NMAs for PFS, OS, Grade 3 to 4 AEs and TRAEs, discontinuation due to AEs and TRAEs (CS; Section B.2.9.1.2, Section B.2.10.2.1 and Appendix D.4.1.5). PFS NMAs The company included data for BICR-assessed PFS from the RELATIVITY-047 trial with data for investigator-assessed PFS from the other three trials[17-19] (Clarification Question A5 and Clarification Question A12). The company did not conduct NMAs to estimate time-varying and constant HRs using RELATIVITY-047 trial investigator-assessed PFS (Clarification Question A9) becausethe company: • considered investigator-assessed PFS was biased [redacted] in the RELATIVITY-047 trial • perceived high concordance of BICR-assessed and investigator-assessed PFS data in both the RELATIVITY-047 trial (Clarification Question A5) and the KEYNOTE-006 trial.[19,49]	The company did not conduct ORR or PRO NMAs. The EAG has performed ORR NMAs (Appendix 4, Section 1.1, Table 64). The EAG considers that it is not possible to conduct meaningful PRO NMAs due to the use of different PRO scales and different measurement times across the four trials.[16-19] PFS NMA The company stated (Clarification Question A5) that BICR-assessed PFS and investigator-assessed PFS are separate outcomes of the RELATIVITY-047 trial (i.e., the primary outcome for which the trial was powered, and an exploratory outcome for which the trial was not powered respectively). Therefore, the EAG considers that the company PFS NMAs, which included data from both BICR-assessed PFS and investigator-assessed PFS are inappropriate and will be impacted by the heterogeneity introduced by the different outcome definitions and assessment methods used. The EAG acknowledges that NMAs of objective BICR-assessed outcomes would remove the risk of investigator bias. However, it was not possible to perform BICR-assessed PFS NMAs that include all four trials[16-19] as the CheckMate 067 trial[17] and the CheckMate 069 trial[18] reported only investigator-assessed PFS. The EAG has therefore performed NMAs using investigator-assessed PFS for all four trials[16-19] to estimate constant HRs (Section 3.7.4). Without access to PLD or K-M data for investigator-assessed PFS in the RELATIVITY-047 trial, the EAG is unable to perform NMAs to estimate time-varying HRs.

Item	EAG assessment	Summary of company approach	EAG comments
Were the networks of comparators appropriate?	Yes	The company search process identified 16 RCTs[16-31] that met the SLR inclusion criteria. The company excluded 12 trials[20-31] which investigated treatments which were not relevant to the decision problem (CS, Table 1) and included four trials[16-19] in their NMAs (CS, Section B.2.1, Appendix D.1.1). The network for company NMAs of PFS, OS and safety outcomes included (CS, Figure 7): • nivolumab-relatlimab (1 trial)[16] • nivolumab+ipilimumab (2 trials)[17,18] • nivolumab (3 trials)[16] • pembrolizumab (1 trial)[19] • ipilimumab (3 trials).[17-19]	The EAG agrees with the inclusion of trials including only treatments which are relevant to the decision problem. The EAG acknowledges that it is necessary to include ipilimumab, which is not relevant to the decision problem, to form a connected network (CS, Figure 7). The EAG considers that the network for the company NMAs was appropriate and included all relevant comparators.
Was the PH assumption appropriately assessed within the NMAs of PFS and OS?	Yes	The company assessed the PH assumption for PFS and OS in the included trials using plots of Schoenfeld residuals versus time and the Grambsch-Therneau test[53] of PH (CS, Appendix D 4.1.2 and Clarification Question A11). Based on these assessments, the company considered that there is uncertainty whether the PH assumption holds for all trials (CS, Section B.2.9.1.1.2) and that there was evidence that the PH assumption was violated for OS and PFS in the CheckMate 067 trial[17] (CS, Section B.2.9.1.1.2, Appendix 4.1.2). Due to these PH violations, in addition to PFS and OS NMAs estimating constant HRs, the company also used FP models to estimate time-varying HRs in their PFS and OS NMAs.	The EAG agrees with the company assessments of PH violation for the trials included in the NMAs. The EAG also agrees with the company that, due to the CheckMate 067 PH violations (which mean constant HR NMAs are not appropriate), estimating time-varying HRs (i.e., FP NMAs) for PFS and OS is appropriate. However, the EAG considers that due to difficulties in interpreting FP NMA results (Section 3.7.1), it is informative to present both sets of results.
Was inconsistency appropriately assessed in the NMAs?	No	The company acknowledged that there was a closed loop of evidence in the network (CS, Figure 7) but considered that the network was, by definition, consistent as the closed loop came from the CheckMate 067 trial,[17] a three-arm trial (Clarification Question A15).	The EAG agrees with the company that performing 'local' (i.e., loop based) inconsistency assessments would automatically demonstrate consistency as the closed loop was the result of a three-arm trial.[17] However, 'global' assessments of inconsistency can still be performed; these examine inconsistency across the whole network. The EAG has performed a 'global' assessment of inconsistency in the EAG NMAs by applying an unrelated mean effects NMA model[56] and by comparing model fit statistics of inconsistency models with consistency models (see Appendix 5, Section 8.5). The EAG is satisfied that no important inconsistency was present in the NMAs of efficacy and safety outcomes.
Were NMA methods	Partly	<u>All company NMAs</u> The methods used in the company NMAs were described in	<u>All company NMAs</u> The EAG considers that the company correctly implemented the

Item	EAG assessment	Summary of company approach	EAG comments
appropriate?		the CS (Section B2.9.1.1.2, Appendix D.4.1) and in response to company Clarification Questions A14 and C7). The company performed NMAs in a Bayesian framework implemented via the rjags package[57] in R version 4.1.3. Although the company considered that the assumptions of RE models were more plausible than the assumptions of FE models, as a small number of trials were included in the NMAs with insufficient data present to estimate heterogeneity variance (Section B.2.9.1.1.2), FE models were presented for all NMAs of efficacy and safety outcomes. <u>Time-varying PFS and OS NMAs</u> For OS and PFS, the company conducted NMAs estimating 1st order (p1=0 [equivalent to a Weibull model]) or p1=1 [equivalent to a Gompertz model]) and 2nd order (p1=0 or 1 and p2=-1, 0.5, 0, 0.5, or 1) FP NMAs according to the methods of Jansen,[58,59] to estimate time-varying HRs due to PH assumption violation within the included trials. Model fit was assessed according to the DIC statistic followed by the fit of FP curves to K-M data and clinical plausibility of extrapolation estimates of the top two best fitting models for PFS and top four best fitting models according to DIC (Clarification Question A10). The company selected the 2nd best fitting FP model according to DIC for the OS NMAs as the only one of four FP models considered to provide plausible survival curves, particularly for pembrolizumab. Similarly, the company selected the best fitting FP model according to DIC for the PFS NMAs and judged the 2nd best fitting FP model to provide implausible HRs favouring nivolumab over nivolumab-relatlimab after 18 months (Clarification Question A10).	methods described. The EAG also considers that the safety NMAs were correctly implemented. The EAG agrees with the company that RE models are more clinically plausible than FE models due to the heterogeneity in the evidence base (see Section 3.7.1) but acknowledges the instability of results of RE NMAs, due to the small number of included trials and sparse data. The EAG was also unable to estimate heterogeneity variance required for RE model convergence when performing NMAs. However, it should be noted when interpreting company and EAG FE NMA results that FE NMAs do not take account of observed heterogeneity between the trials. <u>Time-varying PFS and OS NMAs</u> The EAG considers that while DIC statistics allow for comparison of the fit of different models, they do not provide information about whether a model is a good fit to the data or whether the estimates generated by the model, including projections of results beyond the follow-up times of trials included in the NMA, are clinically plausible. Furthermore, flexible models which appear similar according to DIC statistics may generate very different long-term survival estimates. This was demonstrated by the company approach when selecting an FP model which provided clinically plausible results for both PFS and OS, all other FP models considered with less than 3 points difference in DIC were judged to produce clinically implausible results. The EAG considers that selection of FP models should primarily be based on clinical plausibility of the estimates generated by the model and the projections of results beyond the follow-up times of trials included in the NMA, rather than primarily based on model fit statistics. The EAG considers that interpretation of estimates provided by FP NMAs can be difficult and are often not intuitive,[60,61] particularly for long-term survival estimate results beyond the follow-up times of trials included in the NMAs. Applying the methods as described by Jansen 2011[59] and Jansen 2012[58] means that the width of the 95% CrIs around the time-varying HRs remains approximately the same at all time points. The 95% CrIs do not reflect the number of patients providing data at each time point (which diminishes over time); rather, they reflect the amount of data available overall. The EAG does not consider that it is appropriate to infer statistical significance (or lack of) from the 95% CrIs of FP NMAs.

Item	EAG assessment	Summary of company approach	EAG comments
Was the presentation of NMA and results appropriate?	Yes	The company presented FE NMA results for nivolumab-relatlimab versus nivolumab+ipilimumab, pembrolizumab and nivolumab as time-varying HRs (with 95% CrIs) for PFS (CS, Table 17, Figure 8 and Figure 9) and OS (CS, Table 18, Figure 11 and Figure 12). The company presented FE NMA results for nivolumab-relatlimab versus nivolumab+ipilimumab and pembrolizumab as constant HRs (with 95% CrIs) for PFS and OS (CS, Appendix D, Table 15 and Table 16) and ORs (with 95% CrIs) for safety outcomes (CS, Section B.2.10.2.1).	The presentation of company NMA results for all outcomes is appropriate. The EAG has presented results for all pairwise comparisons of the interventions included in the network for EAG NMAs of PFS and OS (constant HRs), ORR and safety outcomes (Table 20 and Appendix 4, Section 8.4, Table 64). Company and EAG NMAs using FE models only are presented. The EAG acknowledges the instability of results of RE NMAs, due to the small number of included trials and sparse data. However, it should be noted when interpreting FE NMA results that FE NMAs do not take account of observed heterogeneity between the trials.

AE=adverse event; BICR=blinded independent central review; CrI=credible interval; CS=company submission; DIC=deviance information criterion; EAG=External Assessment Group; FE=fixed-effects; FP=fractional polynomial; HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis; OR=odds ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazard; PLD=patient level data; PRO=patient reported outcome; RE=random-effects; SLR=systematic literature review; TRAE=treatment-related adverse events
Source: CS, Section B.2.9.1, Section B.2.9.2, Appendix D, Clarification Questions A14 and C7, and includes EAG comment

Table 18 EAG summary and critique of the company statistical approaches to adjusted ITCs

Item	EAG assessment	Summary of company approach	EAG comments
Were adjusted ITCs conducted for all relevant outcomes?	Yes	The company presented adjusted ITCs for BICR-assessed PFS, investigator-assessed PFS, OS, all-cause AEs (any grade and Grade 3 to 4), TRAEs (any grade and Grade 3 to 4), and TRAEs leading to discontinuation of treatment (CS; Section B.2.9.2.1, Section B.2.10.2.1 and Appendix D.4.1.5).	The company did not conduct adjusted ITCs for ORR or PROs. The EAG considers that it is not possible to conduct meaningful adjusted ITCs of ORR or PROs due to the differences in assessment methods, measurement scales and measurement times across the RELATIVITY-047 trial[16] and the CheckMate 067 trial.[17]
Were the networks of comparators appropriate?	Partly	The company conducted adjusted ITCs to compare the relative efficacy and safety of nivolumab-relatlimab and nivolumab+ipilimumab adjusted for potential confounding effects due to differences in treatment effect modifying baseline characteristics using PLD from the RELATIVITY-047 trial[16] and the CheckMate 067 trial.[17]	No adjusted indirect evidence is available for nivolumab-relatlimab compared to pembrolizumab; however, the EAG acknowledges that PLD from the KEYNOTE-006 trial[19] would be required to perform an adjusted ITC of nivolumab-relatlimab compared to pembrolizumab and these data are not publicly available.
Were adjusted ITC methods appropriate?	Yes	The methods used in the company adjusted ITCs are described in the CS (Section B.2.9.2.1, Appendix D.4.2) and the company response to Clarification Questions A14, A16 and C8). The company performed adjusted ITCs of BICR-assessed PFS, investigator-assessed PFS, OS and safety outcomes using PLD from the RELATIVITY-047 trial[16] and the CheckMate 067 trial[17] adjusted using an IPTW approach which aims to balance baseline characteristics by inverse propensity score weighting. Baseline characteristics included in the adjusted analysis were age, sex, geographic region, ECOG PS, time from advanced melanoma diagnosis until randomisation, AJCC metastatic stage with LDH category, AJCC disease stage at study entry, melanoma subtype, *BRAF* mutation status, baseline LDH categories, PD-L1 expression category. Baseline characteristics before and after weighting for nivolumab-relatlimab and nivolumab+ipilimumab and for the nivolumab arms of the two trials[16,17] were presented in the CS, Appendix D (Table 18 and Table 19). The company truncated investigator-assessed PFS and OS data in the CheckMate 067 trial[17] by censoring patients who did not an experience an event by August 2016 (median follow-up 28 months) to align with the median follow-up duration of the RELATIVITY-047 trial data ([redacted]). Safety data from the first 28 months of the trials were used in the adjusted ITC. In the CheckMate 067 trial,[17] BICR-assessed PFS data were available only from the February 2015 data cut-off (minimum 9 months follow-up), therefore data from the RELATIVITY-047 trial October 2021 data cut-off (minimum 9 months follow-up) were used in the adjusted ITC.	Clinical advice to the EAG is that all important potential treatment effect modifiers were included in the adjusted ITCs. The EAG considers that the choice of data cut-offs and truncation of outcome data to align the follow-up times of the RELATIVITY-047 trial[16] and the CheckMate 067 trial[17] for each outcome was appropriate and that the IPTW approach has been correctly implemented. The EAG agrees that following weighting, baseline characteristics for patients in the nivolumab-relatlimab and nivolumab+ipilimumab and for the nivolumab arms of the two trials[16,17] were suitably balanced.

Item	EAG assessment	Summary of company approach	EAG comments
Was the PH assumption appropriately assessed within the adjusted ITCs of PFS and OS?	Yes	The company also assessed the PH assumption for investigator-assessed PFS and OS for the comparison of nivolumab-relatlimab vs nivolumab+ipilimumab and for the comparison of the nivolumab arms in the RELATIVITY-047 trial[16] and the CheckMate 067 trial[17] using plots of Schoenfeld residuals versus time and the Grambsch-Therneau test[53] of PH (Clarification Question A20). The company found no evidence of violation of the PH assumption.	The EAG agrees with the company assessments of PH for the comparisons made in the adjusted ITCs.
Was the presentation of adjusted ITC results appropriate?	Yes	The company presented K-M curves and HRs (with 95% CIs) for investigator-assessed PFS and OS for the nivolumab-relatlimab versus nivolumab+ipilimumab comparison and comparing the nivolumab arms of the two trials[16,17] before weighting (CS, Appendix D, Figure 4 to Figure 7) and after weighting (CS, Section B.2.9.2.2 and Figure 14 to Figure 17). The company presented proportions of patients with all-cause AEs (any grade and Grade 3 to 4), TRAEs (any grade and Grade 3 to 4), and TRAEs leading to discontinuation of treatment for nivolumab-relatlimab and nivolumab+ipilimumab after weighting (CS, Table 23 and Clarification Question A21).	The presentation of company adjusted ITC results for all outcomes is appropriate.

AE=adverse event; AJCC=American Joint Committee on Cancer; BICR=blinded independent central review; CI=confidence interval; CS=company submission; EAG=External Assessment Group; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; IPTW=inverse probability of treatment weighting; ITC=indirect treatment comparison; K-M=Kaplan-Meier; LDH=lactate dehydrogenase; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PH=proportional hazard; PLD=patient level data; PRO=patient reported outcome; PS=performance status; SLR=systematic literature review; TRAE=treatment-related adverse events
Source: CS, Section B.2.9.1, Section B.2.9.2, Appendix D, Clarification Questions A14, A16 and C8, and includes EAG comment

3.7.4 Results from the NMAs

Company time-varying HR NMAs: PFS and OS

Time-varying HRs at 3-month intervals up to 48 months from the company fixed-effects (FE) FP PFS and OS NMAs for nivolumab-relatlimab versus nivolumab+ipilimumab, pembrolizumab and nivolumab are provided in Table 19.

The company considered that the FP NMA results showed no statistically significant differences in PFS and OS for the comparison of nivolumab-relatlimab versus nivolumab+ipilimumab. Nivolumab-relatlimab was associated with a statistically significant PFS improvement versus nivolumab at all time points and versus pembrolizumab at all time points except for at Month 3. Nivolumab-relatlimab was also associated with a numerical (but not statistically significant) OS advantage versus pembrolizumab and versus nivolumab at all time points. The company also considered that FP PFS and OS NMA results for nivolumab-relatlimab versus nivolumab closely align with the results of the RELATIVITY-047 trial (CS, Section 2.9.1.2.1).

The EAG does not consider that it is appropriate to infer statistical significance (or lack of) from the 95% credible intervals (CrIs) of FP NMAs (see Table 17).

Table 19 Company FP NMA results for nivolumab-relatlimab versus nivolumab+ipilimumab, pembrolizumab and nivolumab

Nivolumab-relatlimab versus	Outcome	Time-varying HR (95% CrI)[c]									
		3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Nivolumab+ ipilimumab	PFS[a]	[redacted]									
	OS[b]	[redacted]									
Pembrolizumab	PFS[a]	[redacted]									
	OS[b]	[redacted]									
Nivolumab	PFS[a]	[redacted]									
	OS[b]	[redacted]									

[a] Results are presented for PFS from best fitting second order FP model: P1=1, P2=-0.5; scale and 2nd shape. PFS FP NMAs include BICR-assessed PFS data for the RELATIVITY-047 trial[34] and investigator-assessed PFS data for the other three trials[44,45,49]
[b] Results are presented for OS from best fitting second order FP model: P1=1, P2=--1; scale and 2nd shape
[c] HR<1 indicates an advantage to nivolumab-relatlimab. The EAG does not consider that it is appropriate to infer statistical significance (or lack of) from the 95% CrIs of FP NMAs (see Table 17)
BICR=blinded independent central review; CrI=credible interval; FP=fractional polynomial; HR=hazard ratio; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival
Source: CS, Table 17 and Table 18

Company and EAG constant HR NMAs: PFS and OS

Results of company constant HR PFS and OS NMAs are presented in the CS, Appendix D (Table 15 and Table 16).

The EAG has replicated the company constant HR NMAs using data presented in Appendix 2 (Section 8.2, Table 61) and the multinma R package.[62] Results of EAG constant HR PFS and OS NMAs are presented in Table 20. EAG constant HR NMA results are very similar to company constant HR NMA results; any observed differences may be due to rounding and/or due to differences in statistical implementation within R.

The EAG has also conducted a constant HR PFS NMA using investigator-assessed data (Table 20). No statistically significant differences for nivolumab-relatlimab versus nivolumab+ipilimumab, versus pembrolizumab or versus nivolumab for investigator-assessed PFS and OS were demonstrated. The constant HR point estimate generated by the EAG PFS NMA (using only investigator-assessed PFS data) is [redacted] (1.12) than the constant HR point estimate generated by the company PFS NMA ([redacted]), which included BICR-assessed PFS data from the RELATIVITY-047 trial (and investigator-assessed PFS from the other three trials)[17-19] and favoured nivolumab+ipilimumab over nivolumab-relatlimab.

Table 20 EAG fixed-effect constant HR NMA results: PFS (BICR and investigator-assessed) and OS

Comparison[a]	HR (95% CrI)		
	BICR / investigator-assessed PFS[b]	Investigator-assessed PFS[c]	OS
Nivolumab-relatlimab vs nivolumab+ipilimumab	1.03 (0.78 to 1.36)	1.12 (0.84 to 1.48)	0.97 (0.71 to 1.31)
Nivolumab-relatlimab vs nivolumab	**0.81 (0.67 to 0.98)**	0.88 (0.73 to 1.06)	0.82 (0.66 to 1.02)
Nivolumab-relatlimab vs pembrolizumab	0.79 (0.57 to 1.13)	0.87 (0.62 to 1.22)	0.70 (0.49 to 1.03)
Nivolumab-relatlimab vs ipilimumab	**0.43 (0.33 to 0.56)**	**0.47 (0.36 to 0.61)**	**0.52 (0.38 to 0.69)**
Nivolumab+ipilimumab vs nivolumab	**0.79 (0.64 to 0.97)**	**0.79 (0.64 to 0.97)**	0.84 (0.68 to 1.04)
Nivolumab+ipilimumab vs pembrolizumab	**0.77 (0.62 to 0.97)**	**0.77 (0.62 to 0.96)**	**0.73 (0.58 to 0.92)**
Nivolumab+ipilimumab vs ipilimumab	**0.42 (0.40 to 0.44)**	**0.42 (0.40 to 0.44)**	**0.53 (0.51 to 0.56)**
Pembrolizumab vs nivolumab	1.02 (0.76 to 1.35)	1.02 (0.76 to 1.35)	1.16 (0.85 to 1.57)
Nivolumab vs ipilimumab	**0.53 (0.44 to 0.64)**	**0.53 (0.44 to 0.64)**	**0.63 (0.52 to 0.77)**
Pembrolizumab vs ipilimumab	**0.54 (0.44 to 0.67)**	**0.54 (0.44 to 0.67)**	**0.73 (0.58 to 0.92)**

[a] HR<1 favours the first treatment in the comparison over the second treatment. 95% CrIs that do not cross 1 (i.e., statistically significant) for results are highlighted in **bold**

[b] Summary data for BICR-assessed PFS included from the RELATIVITY-047 trial and investigator-assessed PFS for the CheckMate 067,[17] CheckMate 069[18] and KEYNOTE-006[19] trials

[c] Summary data for investigator-assessed PFS from all trials[16-19]

BICR=blinded independent central review; CrI=credible intervals; EAG=External Assessment Group; HR=hazard ratio; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival

Source: EAG analysis using statistical code in EAG report Appendix 3 (Section 8.3) applied to the data in EAG report Appendix 2 (Section 8.2, Table 61)

Company and EAG safety NMAs

Results of company safety NMAs are provided in the CS (Section B2.10.2.1).

The EAG has replicated the company safety NMAs using data presented in Appendix 2 (Section 8.2, Table 62) and the multinma R package.[62] Results of EAG NMAs are presented in Appendix 4, Section 8.4, Table 64. Results of EAG NMAs are very similar to the results of company NMAs; observed differences may be due to EAG corrections made to summary data included in the NMAs (see Appendix 2, Section 8.2, Table 62 footnotes of rounding of summary data) and due to differences in statistical implementation within R.

Results of company and EAG NMAs show that, compared with nivolumab+ipilimumab, patients treated with nivolumab-relatlimab have statistically significantly lower odds of Grade 3 to 4 AEs and Grade 3 to 4 TRAEs, discontinuations due to AEs and discontinuations due to TRAEs. EAG NMA results also show that, compared to pembrolizumab, treatment with nivolumab-relatlimab leads to statistically significantly higher odds of Grade 3 to 4 TRAEs and higher odds (although not statistically significantly higher) of discontinuations due to AEs and discontinuations due to TRAEs.

3.7.5 Efficacy and safety results from the adjusted ITCs

Adjusted ITC efficacy results

Efficacy results from the company adjusted ITCs for investigator-assessed and BICR-assessed PFS and OS are provided in Table 21.

Table 21 Efficacy results from the company adjusted ITCs: PFS and OS

Outcome	Nivolumab-relatlimab (RELATIVITY-047)	Nivolumab+ ipilimumab (CheckMate 067)	Nivolumab (RELATIVITY-047)	Nivolumab (CheckMate 067)
Effective sample size[a]	[redacted] ([redacted] excluded)	[redacted] ([redacted] excluded)	[redacted] ([redacted] excluded)	[redacted] ([redacted] excluded)
Investigator-assessed PFS	HR (95% CI): [redacted] K-M curve: CS, Figure 12		HR (95% CI): [redacted] K-M curve: CS, Figure 14	
BICR-assessed PFS	HR (95% CI): [redacted] K-M curve: Clarification Question A17, Figure 30		NR	
OS	HR (95% CI): [redacted] K-M curve: CS, Figure 13		HR (95% CI): [redacted] K-M curve: CS, Figure 15	

[a] Effective sample size after weighting; patients with missing data for specified covariates and patients with inverse probability of treatment weights <5% or >95% percentile excluded
BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; K-M=Kaplan-Meier; NR=not reported; OS=overall survival; PFS=progression-free survival
Source: CS, Section B2.9.2.2.2, Appendix D, Table 18 and Table 19, Clarification Question A17, A19 and C9

Adjusted ITC safety results

Adjusted safety outcome ITC results are provided in the CS (Table 23) and in the clarification response (Clarification Question A21). [redacted] proportions of AEs and TRAEs, Grade 3 to 4 AEs and Grade 3 to 4 TRAEs and discontinuations due to TRAEs were observed for nivolumab+ipilimumab compared to nivolumab-relatlimab (CS, Table 23) and also for nivolumab in the CheckMate 067 trial[17] compared to nivolumab in the RELATIVITY-047 trial (Clarification Question A21). The company considered that, "improvements in AE management over time may explain differences in observed rates between the trials" for the comparison between nivolumab arms (Clarification Question A21). The EAG considers that if differences in AE management over time influences the comparison between the nivolumab arms of the RELATIVITY-047 trial and CheckMate 067 trial,[17] then AE management would also influence the nivolumab-relatlimab and nivolumab+ipilimumab comparison. However, clinical advice to the EAG is that increased experience in managing AEs is more likely to affect time to resolution of AEs rather than incidence of AEs.

3.8 *EAG clinical effectiveness evidence conclusions*

The EAG notes that the population specified in the final scope issued by NICE differs to the population specified in the company proposed MHRA licence (i.e., [redacted] versus [redacted]) and the European Union approved marketing authorisation (i.e., [redacted] versus [redacted]).

The company identified one trial (the RELATIVITY-047 trial) that compared the efficacy and safety of nivolumab-relatlimab versus nivolumab. The RELATIVITY-047 trial is a well-conducted RCT with low risk of bias that enrolled patients for whom an IO combination therapy was suitable.

In NG14,[9] it is recommended that NHS patients with untreated unresectable or metastatic melanoma:

- for whom IO combination therapy (currently only nivolumab+ipilimumab) is suitable and acceptable, receive nivolumab+ipilimumab
- for whom nivolumab+ipilimumab is **not** suitable or acceptable, receive pembrolizumab or nivolumab.

It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial[17] and CheckMate 069 trial[18]) should be used to inform decision-making for the population for whom nivolumab+ipilimumab is **not** suitable or acceptable as these trials only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable.

RELATIVITY-047 ITT trial results show that, compared with nivolumab, treatment with nivolumab-relatlimab improved PFS and ORR; however, median OS was [redacted] in the nivolumab-relatlimab arm. Patient HRQoL was stable and similar between treatment arms; change from baseline never exceeded the pre-specified MIDs. Clinical advice to the EAG is that there were no unexpected AEs and that the safety profile of nivolumab-relatlimab is manageable.

Direct evidence was not available for the comparison of the clinical effectiveness of nivolumab-relatlimab versus nivolumab+ipilimumab or versus pembrolizumab. The company carried out time-varying HR NMAs (FPs) and constant HR NMAs to compare nivolumab-relatlimab versus nivolumab+ipilimumab, pembrolizumab and nivolumab; three trials [17-19] in addition to RELATIVITY-047 were included in these NMAs. Differences in baseline patient characteristics, trial design, outcome definitions and outcome follow-up periods may have introduced heterogeneity; the impact of any heterogeneity is unknown.

For time-varying HR NMAs, model fit was assessed according to the DIC statistic followed by the fit of FP curves to K-M data and clinical plausibility of extrapolation estimates. The EAG considers that clinical plausibility should be assessed before consideration of DIC statistics. The EAG also considers that 95% CrIs around the time-varying HRs cannot be used to infer statistically significant differences, nor lack of statistically significant difference, nor similarity between nivolumab-relatlimab and pembrolizumab, nor similarity between nivolumab-relatlimab and nivolumab+ipilimumab.

For constant HR NMAs, the EAG was concerned that there was evidence that the PH assumption was violated.

The company time-varying HR NMAs and constant hazard HR NMAs were undertaken using BICR-assessed PFS data from the RELATIVITY-047 trial and investigator-assessed PFS data from the other three trials;[17-19] the EAG considers that this approach was inappropriate given differences in RELATIVITY-047 trial BICR-assessed and investigator-assessed PFS results.

The company carried out adjusted ITCs to compare nivolumab-relatlimab versus nivolumab+ipilimumab; two trials[16,17] were included in the adjusted ITCs. The EAG is satisfied with the methods used by the company to carry out the adjusted ITCs.

The EAG considers the best available evidence provided by the company for comparisons between treatments for PFS and OS are:

- nivolumab-relatlimab versus nivolumab: RELATIVITY-047 trial BICR-assessed and investigator-assessed PFS and OS (treatment with nivolumab-relatlimab improved BICR-assessed PFS)
- nivolumab-relatlimab versus nivolumab+ipilimumab: adjusted ITCs for BICR-assessed and investigator-assessed PFS and OS (no statistically significant differences)
- nivolumab-relatlimab versus pembrolizumab: EAG constant HR NMAs for investigator-assessed PFS and OS (no statistically significant differences); the reliability of these results is limited due to the violation of the PH assumption for the trials included in the constant HR NMAs.

Regarding safety, the evidence from the RELATIVITY-047 trial NMAs and adjusted ITCs suggest that treatment with:

- nivolumab-relatlimab results in more TRAEs (Grade 3 to 4 and discontinuations) than nivolumab
- nivolumab-relatlimab results in fewer TRAEs (Grade 3 to 4 and discontinuations) than nivolumab+ipilimumab
- nivolumab-relatlimab results in more TRAEs (Grade 3 to 4) than pembrolizumab; however, pembrolizumab safety data from the KEYNOTE-006 trial[19] were only available for the overall population which included previously treated patients (34%).

All patients in the included trials were aged >20 years. The company confirmed that there is no nivolumab-relatlimab clinical trial evidence for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma (Clarification Question A3). Therefore, the treatment effect of nivolumab-relatlimab for this subgroup is uncertain.

4. COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of nivolumab-relatlimab for patients with untreated unresectable or metastatic melanoma. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 *Company review of published cost effectiveness evidence*

The company conducted a systematic literature review to identify relevant cost effectiveness studies relating to treatments for advanced melanoma. The database searches were originally completed in January 2022 and then updated in November 2022. Details of the company's systematic review are provided in the CS (Appendix G) and in the clarification response (Clarification Question C10).

The company's searches identified four UK-based studies[63-66] that assessed the cost effectiveness of IO therapies for the treatment of advanced melanoma; details are provided in the CS (Table 24). None of the identified studies evaluated nivolumab-relatlimab as a treatment for previously untreated unresectable or metastatic melanoma.

The company also conducted a manual search of the NICE website in March 2023 to identify relevant HTA submissions. Three technology appraisals (TAs) of relevant comparators were identified (TA366[13] [pembrolizumab]; TA384[12] [nivolumab]; TA400[11] [nivolumab+ipilimumab]), in addition to a melanoma health economic model report (Melanoma health economic modelling report [HEMR]) published by NICE[67] as part of NG14[9] in 2022.

4.1.1 EAG critique of the company's literature review

A summary of the EAG's critique of the company's literature review methods is provided in Table 22.

Table 22 EAG appraisal of company systematic review methods

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Start date of electronic database searches not reported
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Studies of patients <18 years of age (children and young adults) were excluded
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Data were extracted by a single reviewer and validated by a second reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were attempts to synthesise evidence appropriate?	NA

EAG=External Assessment Group; NA=not applicable
Source: EAG in-house checklist

4.1.2 EAG conclusions

The EAG has no major concerns about the search strategies used by the company to identify cost effectiveness studies. However, the electronic database search start dates were not reported. Furthermore, inclusion criteria limited included studies to those enrolling adults (≥18 years of age), which is inconsistent with the population defined in the final scope issued by NICE (people aged 12 years and older); the EAG agrees with the company that it is unlikely that any relevant studies were omitted.

4.2 *EAG summary and critique of the company's submitted economic evaluation*

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 23 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Yes. The company carried out NMAs and adjusted ITCs
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimension; ITC=indirect treatment comparison; NMA=network meta-analysis; PSS=Personal Social Services; QALY=quality adjusted life year
Source: NICE Reference Case[68]

Table 24 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Yes	-
Were all the important and relevant costs and consequences for each alternative identified?	Yes	-
Were costs and consequences measured accurately in appropriate physical units?	Yes	-
Were the cost and consequences valued credibly?	Mostly	Errors relating to healthcare resource use estimates; fixed in company addendum
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	-
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	-
Did the presentation and discussion of study results include all issues of concern to users?	Yes	-

EAG=External Assessment Group
Source: Drummond and Jefferson (1996)[69]

4.2.2 Model structure

The company developed a partitioned survival model with three mutually exclusive health states (progression-free [PF], progressed disease [PD] and death). All patients enter the model in the PF health state and are then at risk of moving to the PD or death health states. Patients in the PD health state are only at risk of moving to the death health state. Patients do not move out of the death health state. The cycle length is 1 month (30.44 day); this is in line with the approach adopted in the NICE Melanoma HEMR report[67] model. An illustration of the company model structure is shown in Figure 1.

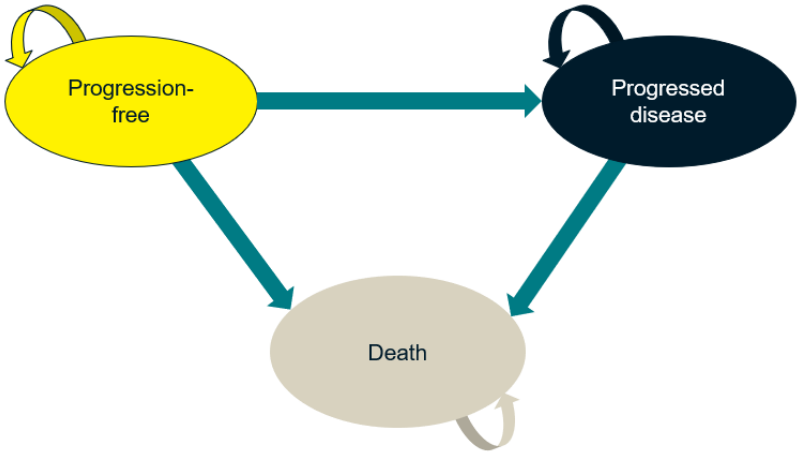

Figure 1 Company model schematic

Source: CS, Section B.3.2.2, Figure 17

4.2.3 Population

[redacted]. The model baseline patient characteristics reflect the RELATIVITY-047 trial baseline population characteristics (Table 25).

Table 25 Model baseline population characteristics (RELATIVITY-047 trial)

Baseline characteristic	Value
Mean age	[redacted]
Mean weight	[redacted]
Proportion male	[redacted]
Body surface area	[redacted]

Source: CS, Table 25

4.2.4 Interventions and comparators

The intervention evaluated in the company model was nivolumab-relatlimab (dosage outlined in Table 26), and the comparators were nivolumab, nivolumab+ipilimumab and pembrolizumab. For all IO therapies, a 2-year stopping rule was applied in line with the NICE Melanoma HEMR and the clinical advice[10] given to the company that treatment would be discontinued for most patients at, or prior to, this timepoint. The pembrolizumab pivotal trial[49] (KEYNOTE-006) was the only study to include a treatment stopping rule.

Table 26 Model intervention and comparator regimens

Treatment	Dosage	Treatment rules applied in model
Nivolumab-relatlimab	640mg Q4W	Maximum treatment duration set to 2 years, consistent with UK clinical advice[10]
Nivolumab+ipilimumab	Nivolumab 1mg/kg + ipilimumab 3 mg/kg Q3W for four cycles (induction period) followed by nivolumab 480mg Q4W (maintenance period)	Maximum treatment duration for nivolumab set to 2 years, consistent with UK clinical advice[10]
Nivolumab	480mg Q4W	Maximum treatment duration set to 2 years, consistent with UK clinical advice[10]
Pembrolizumab	400mg Q6W	Maximum treatment duration=2 years as per pivotal trial (KEYNOTE-006[49]) and consistent with UK clinical advice[10]

Q3W=every 3 weeks; Q4W=every 4 weeks; Q6W=every 6 weeks
Source: CS, Section B.3.2.3 & CS, Table 27

4.2.5 Perspective, time horizon and discounting

The company stated that the model perspective was the NHS and PSS, and the time horizon was 40 years. In line with the NICE Reference Case,[68] costs and outcomes were discounted at a rate of 3.5% per annum.

4.3 *Treatment effectiveness and extrapolation*

To model OS and PFS for patients treated with nivolumab-relatlimab and nivolumab, curves were fitted to RELATIVITY-047 trial OS and PFS patient level data (PLD). To fit the curves, the company used the guidance outlined in the NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14[70] and 21.[71] In addition to standard parametric models, additional flexible piecewise (K-M plus parametric) and spline models were fitted where necessary. The company assessed the suitability of all models by considering:

- assessment of PH
- visual inspection of fit to RELATIVITY-047 trial K-M data
- shape of underlying hazard functions
- statistical goodness of fit indicated by Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) statistics
- validation of extrapolations using UK clinical expert opinion
- comparison with relevant long-term evidence of the effectiveness of immunotherapies as treatments for advanced melanoma.

In the absence of direct head-to-head evidence and evidence of a lack of PHs within the network of evidence, the company's FP NMA results were applied to nivolumab PFS and OS estimates to generate nivolumab+ipilimumab and pembrolizumab PFS and OS estimates.

4.3.1 Overall survival

The RELATIVITY-047 trial OS PH assumption was assessed using Schoenfeld residuals and log-cumulative hazard plots (CS, Appendix O.2.1); however, it was not possible to determine from the results of these analyses whether the PH assumption held. The company therefore generated OS estimates by fitting parametric models to data from each trial arm. The company selected (different) Gompertz distributions to generate OS estimates for patients treated with nivolumab-relatlimab and nivolumab (Table 27). Nivolumab+ipilimumab and pembrolizumab OS estimates were generated by applying FP NMA HRs to the selected (Gompertz) nivolumab OS distribution.

Table 27 Parametric curves used to model overall survival data

Model arms	Base case parametric curves
Nivolumab-relatlimab (RELATIVITY-047 trial)	Gompertz distribution
Nivolumab (RELATIVITY-047 trial)	Gompertz distribution
Nivolumab+ipilimumab	FP NMA (time-varying) HRs applied to nivolumab curve
Pembrolizumab	FP NMA (time-varying) HRs applied to nivolumab curve

FP=fractional polynomial; NMA=network meta-analysis; HRs=hazard ratios
Source: CS, Section B.3.3.3

4.3.2 Progression-free survival

The company assessed the PH assumption using the Schoenfeld residual and log-cumulative hazard plots (CS, Appendix O.2.2) and considered that there was evidence that the PH assumption was violated, indicating that it was necessary to extrapolate PFS for patients treated with nivolumab-relatlimab and nivolumab by fitting parametric distributions to data from both trial arms. The company considered that, for patients treated with nivolumab-relatlimab and nivolumab, the piecewise Gompertz model produced the most accurate PFS rate at 7.5 years when compared with the long-term nivolumab+ipilimumab and nivolumab data from the CheckMate 067 trial[5] (CS, Appendix O.2.2.3, Table 58 and Table 59).

The company modelled PFS for patients treated with nivolumab+ipilimumab and pembrolizumab by applying FP NMA PFS HRs to the selected (piecewise Gompertz) nivolumab BICR-assessed PFS curve (Table 28).

Table 28 Parametric curves used to model progression-free survival

Model arms	Base case parametric curves
Nivolumab-relatlimab (RELATIVITY-047 trial)	Two-piece: • 0-3 months: PFS K-M data • 3+ months: Gompertz distribution
Nivolumab (RELATIVITY-047 trial)	Two-piece: • 0-3 months: PFS K-M data • 3+ months: Gompertz distribution
Nivolumab+ipilimumab	FP NMA (time-varying) HRs applied to nivolumab curve
Pembrolizumab	FP NMA (time-varying) HRs applied to nivolumab curve

FP=fractional polynomial; HRs=hazard ratios; K-M=Kaplan-Meier; NMA=network meta-analysis; PFS=progression-free survival
Source: CS, Section B.3.3.4

4.3.3 Treatment effect waning

The company modelled a natural waning of treatment effect by using general population mortality hazards.

4.4 *Adverse events*

The company modelled the health and cost impact of Grade 3 to 4 TRAEs with an incidence >1% for patients receiving any of the treatments included in the cost effectiveness analysis (from the RELATIVITY-047 trial). The number of TRAEs associated with treatment with nivolumab+ipilimumab and pembrolizumab were sourced from the CheckMate 067 trial[5] and KEYNOTE-006 trial,[49] respectively (CS, Table 40). The number of several TRAEs associated with pembrolizumab (decreased appetite, vomiting, colitis, adrenal insufficiency, increased lipase, alanine transferase increased, aspartate transferase increased) were not reported in the published paper[49] and so were conservatively assumed to have an incidence of 0%.

4.5 *Health-related quality of life*

The company calculated health state utility values based on EQ-5D-3L data collected during the RELATIVITY-047 trial. Utility values were stratified by progression status and did not vary by treatment (Table 29). Clinical experts consulted by the company[10] expected a greater difference in utility estimates between the PF and PD health states but noted that the estimated utility values were consistent with those used in previous NICE technology appraisals for advanced melanoma (Table 29).

Table 29 Summary of utility values for cost effectiveness analysis in advanced melanoma

Source	Intervention	PF health state utility	PD health state utility
RELATIVITY-047	Nivolumab-relatlimab	[redacted]	[redacted]
TA384[12]	Nivolumab	0.79	0.76
TA400[11]	Nivolumab+ipilimumab	0.80	0.76
TA366[13]	Pembrolizumab	0.82	0.71

PD=progressed disease; PF=progression-free
Source: CS, Table 39 and Table 44

Utility decrements for each Grade 3 to 4 TRAE included in the model were sourced from the literature and are presented in the CS (Table 41). The utility decrements were multiplied by the per cycle probability of each TRAE (and its duration) to produce the utility impact per cycle for each treatment (Table 30).

Table 30 Per cycle utility impact of TRAEs

Treatment regimen	Per cycle (month) utility impact
Nivolumab-relatlimab	-0.00011855
Nivolumab	-0.00006234
Nivolumab+ipilimumab	-0.00134380
Pembrolizumab	-0.00005452

Source: CS, Table 42

4.6 *Resource use and costs*

4.6.1 Drug costs

Drug acquisition costs

Modelled dosages align with the regimens outlined in Table 26. The regimen for nivolumab+ipilimumab differs between induction and maintenance periods and therefore per cycle drug acquisition costs were modelled separately for these periods. Unit drug costs for the comparator treatments were sourced from the Monthly Index of Medical Specialities (MIMS[72]) and are presented in Table 31.

Table 31 Drug unit costs

Drug	Form per vial	Quantity per unit	Quantity per unit (mg)	Price per pack	Source
Nivolumab-relatlimab	16mg/ml	20ml	320mg	[redacted]	Confidential PAS price
Nivolumab	10mg/ml	4ml	40mg	£439	MIMS[72] April 2023
		10ml	100mg	£1,097	MIMS[72] April 2023
		24ml	240mg	£2,633	MIMS[72] April 2023
Ipilimumab	5mg/ml	10ml	50mg	£3,750	MIMS[72] April 2023
		40ml	200mg	£15,000	MIMS[72] April 2023
Pembrolizumab	25mg/ml	4ml	100mg	£2,630	MIMS[72] April 2023

MIMS=Monthly Index of Medical Specialities; PAS=Patient Access Scheme
Source: CS, Table 48

Drug administration costs

Drug administration costs (Table 32) are accrued for the duration of treatment.

Table 32 Drug administration unit costs

Administration type	Cost per administration	Source
Oral*	0	Company assumption
Intravenous	£470.62	NHS Reference Costs[73] 2020/21 - Deliver subsequent elements of a Chemotherapy Cycle [SB15Z]
Intravenous (induction)	£526.52	NHS Reference Costs[73] 2020/21 - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance [SB14Z]

*Some subsequent therapies are oral treatments
Source: CS, Table 49

Time on treatment

Treatment-related costs were modelled by fitting standard parametric distributions to RELATIVITY-047 trial nivolumab-relatlimab and nivolumab time to treatment discontinuation (TTD) data. The company used Weibull distributions in the model to generate TTD estimates as these distributions provided the best statistical fit (lowest AIC/BIC values) to nivolumab-relatlimab and nivolumab RELATIVITY-047 trial TTD data and generated estimates that the company considered closely approximated CheckMate 067 trial[5] nivolumab TTD K-M data.

Near-complete ([redacted]) TTD data (5 years) were available from the CheckMate 067 trial.[5] The company used these data to model TTD for the nivolumab component of treatment with nivolumab+ipilimumab. TTD for the ipilimumab component was modelled based on the proportions of patients receiving one, two, three or four doses of ipilimumab reported in the NICE Melanoma HEMR[67] (CS, Table 37). As KEYNOTE-006 trial[49] K-M TTD data were not available, and published papers only report median time on treatment, based on clinical advice that TTD for patients receiving pembrolizumab and nivolumab was highly similar in clinical practice (CS, Table 30), the company set TTD for patients treated with pembrolizumab to equal that for patients treated with nivolumab TTD.

As noted in Section 4.2.4, the company applied a stopping rule at 2 years for all IO therapies; this affects drug administration and acquisition costs. In addition, TTD was capped by PFS as the company considered that, in NHS clinical practice, it was likely that treatment would be discontinued on progression (CS, p117).

Subsequent treatment costs

Data showing the proportions of patients receiving subsequent treatment are displayed in (Table 33). The proportions of CheckMate 067 trial[5] patients receiving subsequent treatment have been used in the company model for patients whose first-line treatments were nivolumab+ipilimumab and nivolumab. As only immature KEYNOTE-006 trial[49] subsequent treatment data are reported, the company has assumed that the proportion of patients receiving subsequent treatment following treatment with pembrolizumab equals the proportion receiving subsequent treatment following nivolumab. This approach is in line with the preferred approach of the NICE Melanoma HEMR[67] Committee. Subsequent treatment data from the RELATIVITY-047 trial are immature. The company has therefore assumed that the proportion of patients receiving subsequent treatment following nivolumab-relatlimab lies between the proportion receiving subsequent treatment after nivolumab (59%) and the proportion receiving subsequent treatment after nivolumab+ipilimumab (46%), i.e., [redacted]%.

Table 33 Proportion of patients receiving subsequent treatment

First-line treatment	Patients receiving subsequent therapy	Source
Nivolumab-relatlimab	[redacted]%	Assumption based on data from CheckMate 067 trial (5-year follow-up)[5]
Nivolumab	59%	CheckMate 067 trial (5-year follow-up)[5]
Nivolumab+ipilimumab	46%	CheckMate 067 trial (5-year follow-up)[5]
Pembrolizumab	59%	Assumed equal to nivolumab

Source: CS, Table 58

Subsequent treatment distributions (i.e., the proportion of patients who receive each possible second-line treatment, provided they initiate subsequent treatment) used in the company model were adapted from the NICE Melanoma HEMR report[67] values. In the NICE Melanoma HEMR report[67] distributions are based on clinical advice about NHS clinical practice. Clinical advice was that:

- patients with *BRAF*-mutant tumours receive targeted treatment irrespective of first-line treatment (dabrafenib+trametinib: 50%; encorafenib+binimetinib: 50%).
- patients with *BRAF*-wild type tumours receive ipilimumab in the second-line setting if previously treated with IO monotherapy or would be enrolled in clinical trials if previously treated with combination IO therapy.

Clinical advice to the company was that chemotherapy is rarely used as a subsequent treatment in NHS clinical practice. The company assumed that as nivolumab-relatlimab and nivolumab+ipilimumab are both combination IO therapies, the choice of subsequent treatments would be similar. The subsequent treatment distributions in Table 34 correspond to the proportions of RELATIVITY-047 trial patients with *BRAF*-mutant ([redacted]) or *BRAF*-wild type tumours ([redacted]).

Table 34 Modelled subsequent treatment distributions by treatment arm

Subsequent treatment	Nivolumab-relatlimab	Nivolumab	Nivolumab+ ipilimumab	Pembrolizumab
Dabrafenib+trametinib	19.26%	19.26%	19.26%	19.26%
Encorafenib+binimetinib	19.26%	19.26%	19.26%	19.26%
Clinical trials (costed as chemotherapy [dacarbazine])	61.48%	NA	61.48%	NA
Ipilimumab	NA	61.48%	NA	61.48%

NA=not applicable
Source: CS, Table 61

The durations of subsequent treatments were taken from the NICE Melanoma HEMR[67] (nivolumab-relatlimab and nivolumab+ipilimumab: 8.81 months; nivolumab and pembrolizumab: 7.77 months) are presented in the CS (Table 62). The subsequent treatment costs applied in the model are provided in Table 35. The company stated that these costs were applied as a one-off cost on treatment discontinuation.

Table 35 Subsequent treatment costs (for patients who receive subsequent treatment)

First-line treatment	Subsequent treatment acquisition costs	Subsequent treatment administration costs
Nivolumab-relatlimab	£37,895.89	£3,798.46
Nivolumab	£62,122.91	£1,293.46
Nivolumab+ipilimumab	£37,895.89	£3,798.46
Pembrolizumab	£62,122.91	£1,293.46

Source: CS, Table 65

4.6.2 Resource use costs

Resource use costs used in the company model are provided in Table 36; costs were calculated using the NICE TA400 appraisal[11] resource use estimates. Resource use costs were stratified by time from treatment initiation as clinical advice to the company was that resource use is de-escalated over time rather than solely determined by progression status. Three one-off resource use costs were applied to account for resource use associated with treatment initiation, palliative care in the 3 months prior to death and terminal care at death.

Table 36 Resource use costs applied in the company model

Health state	Per cycle cost
Year 1	£1,976.40
Year 2	£985.80
Year 3+	£592.20
Treatment initiation (one-off cost)	£1,117.21
Palliative care (applied in 3 cycles prior to death)	£3,496.40
Terminal care (applied at death)	£7,679.48

Source: CS, Table 53 and Table 54

4.6.3 Adverse event costs

Where possible, the company sourced TRAE unit costs from NHS References Costs[73] and Personal Social Services Research Unit[74] costs; where necessary, other sources were used. The costs associated with each TRAE are presented in the CS (Table 55). Each TRAE cost was multiplied by the per cycle probability of each TRAE (and its duration) to produce the cost impact per cycle for each treatment (Table 37).

Table 37 Per cycle Grade 3 to 4 TRAE costs

Treatment regimen	Per cycle (month) cost
Nivolumab-relatlimab	£7.67
Nivolumab	£5.17
Nivolumab+ipilimumab	£126.24
Pembrolizumab	£2.28

Source: CS, Table 56

4.7 *Disease severity modifier*

Expected general population QALYs were calculated using the general population utilities estimated by Hernandez-Alava[75] and Office for National Statistics life tables[76] general population mortality rates. Patient characteristics (mean age and gender proportions) used to calculate the severity modifier were consistent with the values used in the company base case analysis. Expected general and patient population QALYs were discounted at a rate of 3.5% per annum. Results from the company QALY shortfall calculations are presented in Table 38. As all absolute QALY shortfalls are less than 12 and all proportional QALY shortfalls are less than 85%, the company has not applied disease severity multipliers for any treatment comparisons.

Table 38 Company QALY shortfall calculations

Treatment	Starting age, years	Proportion male (%)	Expected total QALYs for the general population	Expected total QALYs for patients with advanced melanoma receiving current treatment	QALY shortfall estimate: absolute/ proportional
Nivolumab-relatlimab	61.2	58.3	11.891	NA	NA
Nivolumab				4.774	7.12 / 59.85%
Nivolumab+ ipilimumab				5.363	6.53 / 54.90%
Pembrolizumab				4.145	7.75 / 65.14%

NA=not applicable; QALYs=quality adjusted life years
Source: CS, Table 66

5. COST EFFECTIVENESS RESULTS

The EAG identified an error relating to health care resource use estimates (Clarification Question C11); the company corrected the error and provided an addendum and an updated model. The updated company base case deterministic cost effectiveness results are presented in Table 39. These results were generated using the list price for pembrolizumab and confidential PAS prices for all company assets.

Table 39 Company base case deterministic cost effectiveness results, full incremental analysis (nivolumab-relatlimab, nivolumab+ipilimumab and nivolumab PAS prices)

Treatment	Total		Incremental		ICER per QALY
	Costs	QALYs	Costs (£)	QALYs	
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	£20,426
Nivolumab+ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years
Source: Company addendum, Table 13

The updated company base case probabilistic cost effectiveness results (1,000 iterations) are presented in Table 40; these results are similar to the company deterministic cost effectiveness results shown in Table 39.

Table 40 Company base case probabilistic cost effectiveness results, full incremental analysis (nivolumab-relatlimab, nivolumab+ipilimumab and nivolumab PAS prices)

Treatment	Total		Incremental		ICER per QALY
	Costs	QALYs	Costs (£)	QALYs	
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	£18,107
Nivolumab+ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	Strictly dominated

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years
Source: Company addendum, Table 5

5.1.1 Deterministic sensitivity analyses

Using PAS prices for all BMS assets, the company carried out one-way sensitivity analyses (OWSAs), setting values for all parameters with univariate uncertainty distributions to their upper and lower limits. For all three comparisons, PF and PD utility values had the biggest effect on cost effectiveness results. The tornado diagram for the comparison of nivolumab-relatlimab versus nivolumab+ipilimumab is shown in Figure 2; tornado diagrams for the comparison of nivolumab-relatlimab versus nivolumab and versus pembrolizumab are provided in the company addendum (Figure 8 and Figure 10, respectively).

Figure 2 Deterministic sensitivity analysis tornado diagram: nivolumab-relatlimab versus nivolumab+ipilimumab (PAS prices for company assets)

CT=computerised tomography; HCRU=healthcare resource use; ICER=incremental cost-effectiveness ratio; OWSA=one-way sensitivity analysis
Source: Company addendum, Figure 9

5.1.2 Scenario analyses

Using PAS prices for company assets, the company carried out a range of deterministic scenario analyses (CS, Table 85) to explore the effect of changing different model input parameters and model settings. The resulting tornado diagram for the comparison of nivolumab-relatlimab versus nivolumab+ipilimumab is shown in Figure 3; tornado diagrams for the comparison of nivolumab-relatlimab versus nivolumab and versus pembrolizumab are provided in the company addendum (Figure 14 and Figure 16, respectively).

Figure 3 Scenario analysis tornado diagram: impact on ICER for nivolumab-relatlimab versus nivolumab+ipilimumab (PAS prices for company assets)

HEMR=health economic modelling report; OS=overall survival; PFS=progression-free survival; TTD=time to treatment discontinuation
Source: Company addendum, Figure 15

5.1.3 Subgroup analyses

No subgroup analyses were considered.

5.2 *Validation*

The company sought validation of modelling assumptions and inputs from clinical and health economic experts during an HTA Advisory Board meeting to ensure that the model was relevant to UK clinical practice. A quality control check was conducted by an independent health economist using publicly available checklists, including Drummond,[69] Phillips[77] and TechVER.[78] Estimates from both the health economic model and the company NMAs were also compared with data from relevant clinical trials, to ensure predictions were plausible.

6. EAG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 *Introduction*

The company model, developed in MS Excel, compares treatment with nivolumab-relatlimab versus nivolumab+ipilimumab, nivolumab and pembrolizumab for patients with untreated unresectable or metastatic melanoma. As noted in Section 2.3.2, Section 3.7.1 and Section 3.8, the EAG considers that the company and EAG cost effectiveness results only relate to patients for whom an IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) is considered suitable and acceptable.

The EAG identified an error relating to health care resource use estimates (Clarification Question C11); the company corrected this error and provided an addendum and an updated model.

The EAG is satisfied that the company model algorithms are accurate and that parameter values in the model match the values presented in the CS (with the exception of a typographical error that affected AE costs).

A summary of the modelling issues identified by the EAG is shown in Table 41.

Table 41 Summary of EAG company model critique

Aspect considered	EAG comment	Section of EAG report
Population	• The company model population matches the population defined in the NICE scope. However, the EAG considers that the company and EAG cost effectiveness results only relate to patients for whom an IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) is considered suitable and acceptable.	NA
Comparators	• The comparators included in the company model represent SoC for NHS patients with untreated unresectable or metastatic melanoma.	NA
Modelling OS and PFS	• Company OS estimates for patients treated with nivolumab-relatlimab and nivolumab, and PFS for patients treated with nivolumab-relatlimab, do not reflect the underlying hazard profiles from the RELATIVITY-047 trial nor do they have face validity compared to CheckMate 067 trial (7.5 year OS follow-up)[44] data. The EAG has presented alternative OS and PFS modelling scenarios.	6.3.1 6.3.2
Data sources (OS and PFS)	Due to EAG concerns about the company OS and PFS FP and constant hazard NMAs, the EAG considers that the best available evidence for PFS and OS for each modelled treatment is as follows: • nivolumab-relatlimab: RELATIVITY-047 trial • nivolumab: RELATIVITY-047 trial • nivolumab+ipilimumab: adjusted ITCs applied to selected nivolumab-relatlimab extrapolation • pembrolizumab: RELATIVITY-047 trial nivolumab arm	6.4 See also: 3.7 and 3.8

Aspect considered	EAG comment	Section of EAG report
TTD	• The EAG removed the 2-year stopping rules for all IO therapies and amended the nivolumab+ipilimumab TTD data after [redacted] years (the maximum observed follow-up for nivolumab+ipilimumab TTD data from CheckMate 067 in the model) to make the approach to modelling TTD more consistent with the approach used to model TTD for the other treatments. • Clinical advice to the EAG is that in NHS clinical practice treatment may continue beyond disease progression. The EAG has, therefore, removed the constraint that capped TTD by PFS	6.5
Treatment costs	• For most treatments, the company used RDI values of 100%. Data from previous appraisals and the RELATIVITY-047 trial CSR suggest that RDI is likely to be lower than 100%. NHS treatment costs may be lower than company model estimates. The impact on cost effectiveness results is uncertain.	NA
Resource use	• The EAG considers that different IV administration costs should have been used.	6.9
Subsequent treatments	• The EAG considers that some patients who received nivolumab-relatlimab in the first-line setting would receive second-line treatment with ipilimumab monotherapy.	6.6
Utility values	• The utility values used in the company base case conform to the NICE Reference Case[68] and the EAG is satisfied with the model selection process outlined in company clarification response.	6.8
Adverse events	• Patients treated with nivolumab+ipilimumab only receive ipilimumab for three model cycles. The company has applied evidence on rates of AEs from long-term follow-up of the CheckMate 067 trial (minimum 60 months follow-up), which panyhe cominclude outcomes for patients after stopping ipilimumab. The EAG has assumed that once treatment with ipilimumab has ceased, only the costs and disutilities associated with treatment with nivolumab are applied in the model.	6.7
Company disease severity modifier	• A minor company calculation error underestimated the expected general population QALYs; no disease severity modifier is required.	6.11.1
PSA	• FP NMA model parameters were sampled independently; this ignores the correlation between the parameters (d0 and d2); this only affects the company base case probabilistic results.	NA

AE=adverse events; BICR=blinded independent central review; EAG=External Assessment Group; FP=fractional polynomial; HCRU=healthcare resource use; HRs=hazard ratios; IA=investigator-assessed; ITC=indirect treatment comparison; IV=intravenous; NMA=network meta-analysis; OS=overall survival; PSA=probabilistic sensitivity analysis; PFS=progression-free survival; QALYs; quality adjusted life years; RDI=relative dose intensity; TTD=time to treatment discontinuation

6.2 *Company approach to modelling long-term survival (PFS and OS)*

6.2.1 Critique of methods

The company has assumed that some patients who present with untreated unresectable or metastatic melanoma will eventually, regardless of which treatment they receive, have no risk of progression and will have a risk of death similar to the general population. This assumption has generally been accepted in the literature and by previous NICE Appraisal Committees. These patients are described by the company as experiencing long-term survival. This concept is key to understanding the overall approach taken by the company for PFS and OS and underpins the EAG's wider critique of the company survival modelling.

The company notes (CS, Section B.3.3.2.1) that as a subset of patients will experience long-term survival, a mixture-cure model approach to modelling OS and PFS could be explored. However, the company reports that such an approach was "not considered due to the immaturity of RELATIVITY-047" (CS, page 92). The company considered that using parametric extrapolations (either fully parametric or parametric curves appended to K-M data) was the most appropriate way to model survival outcomes.

The company followed DSU guidance[70,71] and used Gompertz distributions to extrapolate RELATIVITY-047 trial nivolumab-relatlimab and nivolumab PFS and OS data. For each treatment and outcome, the company chose independently-modelled Gompertz distributions as they represented the only ones that tended towards a plateau. The company considered that the extrapolations generated by the Gompertz distributions provided the most appropriate model for the underlying hazards in the data and were the only ones to provide clinically plausible extrapolations.

The EAG notes that the company does not define what it means by a plateau or how such a plateau might be distinguished from other survival patterns. However, the company states that analysis of the CheckMate 067 trial[44] data indicates that "the intersection with general population mortality occurs within the trial follow-up [which]… convincingly demonstrates that long-term survival similar to that of the general population occurs for patients with advanced melanoma who are treated with immunotherapies" (CS, page 90) and that "[KEYNOTE-006 and CheckMate 067[44]] also demonstrate plateaus in both OS and PFS, consistent with the concept of long-term survivorship in advanced melanoma following treatment with immunotherapy" (CS, page 92). The EAG thus considers the company uses the term 'plateau' (or long-term survival or long-term survivorship) to indicate that hazards in the trial data are the same as background mortality hazards; in a mixture-cure model, these patients would be described as a 'cured' population.

The EAG considers that, if trial data are sufficiently mature that a fitted Gompertz model that tends towards a plateau (defined as tending towards background mortality hazards) can provide an appropriate representation of a population with long-term survival, then those same data should be sufficiently mature to support a mixture-cure model.

6.2.2 Critique of results generated by company modelling of PFS and OS

When independently modelling PFS and OS for the same population, consideration should be given to the internal validity of the assumptions implied by the chosen models in comparison to one another. Because PFS and OS are modelling outcomes for the same cohort, and therefore PFS is a subset of OS, there should be logical consistency and plausibility in the assumptions for both outcomes. This is particularly clear when using 'cure' models as, for instance, it would be illogical to choose an OS model that predicts fewer patients are 'cured' than the PFS model chosen for the same cohort.

The EAG considers that the proportion of patients alive and progression-free or alive at the timepoint when background mortality hazards are used in the model can be considered the 'cure' proportion from a non-mixture cure model or an appropriate proxy for a 'cure' proportion from a mixture cure approach. In a mixture cure approach, few 'cured' patients would be expected to have died by the point at which PFS or OS hazards meet background mortality hazards; therefore the 'cure' proportion will not differ substantially from the proportions event free at these times. In the absence of explicit 'cure' proportions from the company modelling, the EAG has used these proportions to check whether the comparisons between outcomes and between treatments have face validity.

The EAG considers that, in the company base case, the magnitude of the differences, between treatments, in the proportion of patients 'cured' in the PD health state (Table 42) is implausible as subsequent treatments are expected to be similar for all patients, regardless of initial treatment.

Table 42 Proportion of patients 'cured': company base case analysis

Treatment	Proportion of patients 'cured'*		
	Before progression	After progression	All patients
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]
Nivolumab+ipilimumab	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]

* 'Cure' proportion defined as the time from which background mortality hazards are used in the model

6.3 *EAG revisions: nivolumab-relatlimab and nivolumab survival modelling*

6.3.1 PFS

Information provided in response to Clarification Question A5 suggests that RELATIVITY-047 trial nivolumab arm BICR- and investigator-assessed PFS are different (median BICR-assessed PFS: [redacted] months; median investigator-assessed PFS: [redacted] months. RELATIVITY-047 trial BICR-assessed PFS data were used in the company base case analysis. The EAG considers that investigator-assessed PFS data are more likely to reflect the experience (costs and outcomes) of NHS patients than BICR-assessed PFS data. The EAG requested investigator-assessed PFS K-M data during the clarification process (Clarification Question A4); this was not provided. In the absence of RELATIVITY-047 trial K-M data, the EAG digitised the RELATIVITY-047 trial investigator-assessed PFS data presented in the CS (Appendix D, Figure 4 and Figure 6) and reconstructed the PLD using the Guyot algorithm (Figure 4 and Figure 5).

Figure 4 BICR- and investigator-assessed PFS, nivolumab, RELATIVITY-047 trial

Source: CS, Appendix D, Figure 4 (EAG reproduction)

Figure 5 BICR- and investigator-assessed PFS, nivolumab-relatlimab, RELATIVITY-047 trial

Source: CS, Appendix D, Figure 6 (EAG reproduction)

The EAG followed DSU guidance to select the most appropriate approach(es) to generating investigator-assessed PFS estimates. Based on the guidance, the EAG identified that the most appropriate approach was to append Gompertz distributions, at 3 months, to nivolumab-relatlimab and nivolumab investigator-assessed (EAG digitised) PFS K-M data. In line with the company base case, background mortality hazards are applied from the timepoint when model hazards fall below background mortality hazards to produce the final PFS estimates (

Figure 6). Full details are included in Appendix 6 (section 8.6).

The EAG compared the hazards generated by the EAG investigator-assessed PFS model with RELATIVITY-047 trial and CheckMate 067 trial[44] hazards to assess plausibility. Full details are included in Appendix 6 (section 8.6). The EAG is satisfied that, for both nivolumab-relatlimab and nivolumab, modelling investigator-assessed PFS using a Gompertz distribution appended to K-M data produces outcomes with face validity. The EAG cautions that since there is substantial right censoring after [redacted] (RELATIVITY-047 trial minimum trial follow-up), all PFS estimates are uncertain after this timepoint.

Figure 6 Nivolumab-relatlimab and nivolumab investigator-assessed PFS: EAG K-M plus Gompertz model

Source: EAG modelling

Compared to the company BICR-assessed PFS estimates, the EAG investigator-assessed PFS estimates lead to smaller absolute differences, between all treatments, in the proportions of patients expected to be 'cured' in the PD health state (Table 43).

Table 43 Proportion of patients 'cured': company base case and EAG PFS revisions

Treatment	Proportion of patients 'cured'*					
	Company base case			EAG PFS revisions		
	Before progression	After progression	All patients	Before progression	After progression	All patients
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab+ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* 'Cure' proportion defined as the time from which background mortality hazards are used in the model
EAG=External Assessment Group; PFS=progression-free survival

The EAG acknowledges that the company and EAG approaches to modelling PFS have limitations; nevertheless, the EAG considers that results generated by the EAG approach are more informative than company results.

6.3.2 OS

RELATIVITY-047 trial OS data median follow-up is [redacted] months (October 2022 data lock); there are few OS events and heavy censoring. The EAG therefore considers that any long-term OS estimates are uncertain and the point when background mortality is reached is unknown. Evidence from the CheckMate 067 trial[44] suggests that background mortality is reached for patients treated with nivolumab+ipilimumab and nivolumab at approximately 5 years (Figure 7) and so modelling a proportion of patients being 'cured' is not implausible. However, within the constraints of the structure of a partitioned survival model and in the absence of more mature OS data to inform a cure model, the EAG has been unable to provide more reliable OS estimates.

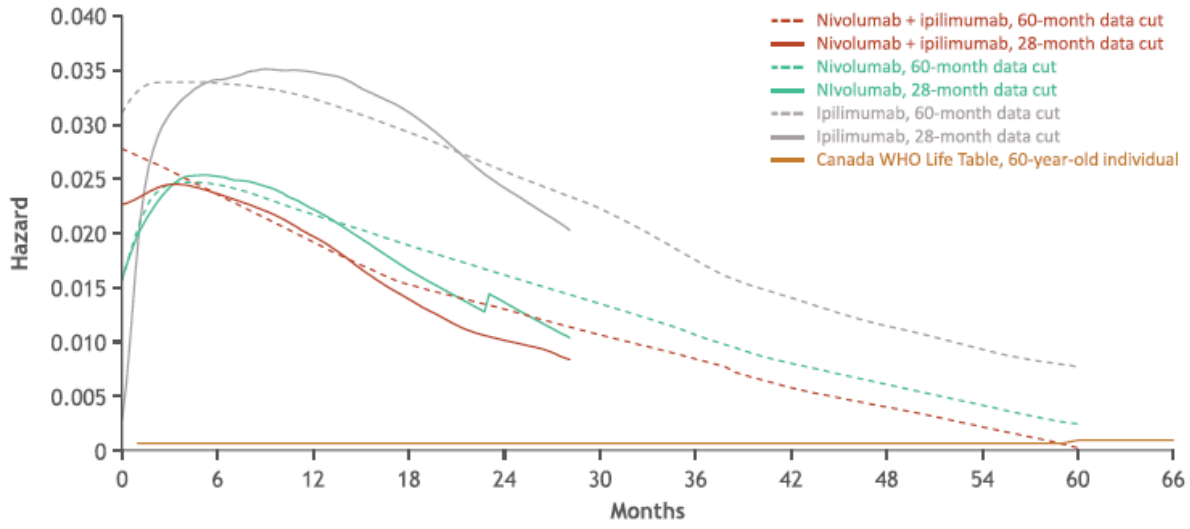

Figure 7 Long-term observed hazards of mortality from CheckMate-067

Source: CS, Figure 20

6.4 *PFS and OS: nivolumab+ipilimumab and pembrolizumab*

The company used PFS and OS FP NMA HRs to model long-term outcomes for patients treated with nivolumab+ipilimumab and for pembrolizumab. The EAG considers that the company FP NMAs should not be used to generate clinical effectiveness results (Section 3.8) Consequently, the EAG does not consider that the company PFS and OS FP NMA results should be used in the company model. The company also provided a scenario analysis using constant HR NMA results to estimate PFS and OS for patients treated with nivolumab+ipilimumab and for pembrolizumab. However, due to the violation of the PH assumptions, the EAG considers that these results may not be reliable.

6.4.1 Nivolumab-relatlimab versus nivolumab+ipilimumab

The company carried out adjusted ITCs to compare the clinical effectiveness of nivolumab-relatlimab versus nivolumab+ipilimumab. There was no evidence of PH violation in any of the trials included in the company adjusted ITCs (CS, Section B.2.9.2.2.2). The EAG therefore considers that the adjusted ITC results (investigator-assessed PFS and OS) should be used in the model. The EAG has carried out a scenario analysis using the adjusted ITC results.

The company states that constant HR NMA and adjusted ITC results demonstrate that nivolumab-relatlimab and nivolumab+ipilimumab have similar efficacy in terms of PFS and OS (CS, p75). Clinical advice to the EAG, however, is that currently the evidence to support similar efficacy is limited. The EAG has undertaken an exploratory analysis to assess the impact on model outcomes of assuming that BICR-assessed PFS and OS for nivolumab+ipilimumab are equal to BICR-assessed PFS and OS for nivolumab-relatlimab. For consistency, in this scenario, nivolumab+ipilimumab TTD was set equal to nivolumab-relatlimab TTD.

6.4.2 Nivolumab-relatlimab versus pembrolizumab

Pembrolizumab PLD data were not available and therefore pembrolizumab could not be included as a comparator in the company adjusted ITCs. The only other comparative evidence for nivolumab-relatlimab versus pembrolizumab is from the company constant HR and FP NMAs. The EAG considers that the best available evidence for this indirect comparison is from the EAG constant HR NMAs for investigator-assessed PFS and OS (no statistically significant differences); however, the reliability of this result is limited due to the violation of the PH assumption for the trials included in the constant HR NMAs.

Clinical advice to the company (CS, p103) and to the EAG is that, overall, the efficacy and safety profiles of pembrolizumab and nivolumab are similar. The EAG has set PFS and OS for pembrolizumab equal to PFS and OS for nivolumab (RELATIVITY-047 trial).

Compared with the company base case, the EAG PFS and OS revisions combined with revisions to assumptions around the relative treatment effect for nivolumab+ipilimumab (adjusted ITC) and pembrolizumab (equal to nivolumab) result in similar cure rates after progression for IO combination treatments and for IO monotherapies (Table 44).

Table 44 Proportion of patients experiencing a cure: company base case, and EAG combined PFS, OS, NMA and ITC revisions for all treatments

Treatment	Proportion of patients 'cured'*					
	Company base case			EAG PFS, OS, NMA and ITC revisions		
	Before progression	After progression	All patients	Before progression	After progression	All patients
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab+ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* 'Cure' proportion defined as the time from which background mortality hazards are used in the model
EAG=External Assessment Group; ITC=indirect treatment comparison; OS=overall survival; NMA=network meta-analysis; PD=progressed disease; PFS=progression-free survival

6.5 *Treatment cost and duration*

6.5.1 Treatment beyond progression

In the company base case, a constraint is applied so that TTD cannot exceed PFS, i.e., no patients remained on first-line treatment beyond disease progression. The company stated that this is in line with UK clinical practice (CS, p117). The company considered, based on BICR-assessed PFS, that this constraint was conservative as a higher proportion of RELATIVITY-047 trial patients in the nivolumab arm remained on treatment post-progression than in the nivolumab-relatlimab arm (Clarification Question A2). Clinical advice to the EAG is that NHS patients are treated post-progression if there is evidence of clinical benefit (symptoms reduced or very slowly progressing). The EAG therefore considers that treatment costs are more accurately estimated by removing the constraint capping TTD by PFS.

6.5.2 Treatment stopping rules

In the company base case analysis, in line with the NICE Melanoma HEMR and clinical opinion[10] was that less than 10% of patients remain on IO therapies after 2 years, the company implemented a 2-year treatment stopping rule for all IO therapies. This approach is consistent with clinical advice to the EAG that treatment is typically discontinued at, or prior to, 2 years due to the toxicity associated with IO therapies. However, the EAG notes that a stopping rule was not implemented in the RELATIVITY-047 trial and is not specified in the EU marketing authorisation[7] for nivolumab-relatlimab (CS, Table 2). In addition, no stopping rules were specified in the NICE recommendations for nivolumab,[12] pembrolizumab[13] or nivolumab+ipilimumab[11] as treatments for advanced melanoma.

Neither the RELATIVITY-047 trial nor the CheckMate 067 trial[44] included a stopping rule and a significant proportion of patients remained on treatment at 2 years (Table 45). The EAG has therefore removed all the treatment stopping rules in the company model.

Table 45 Trial treatment stopping rules

Study	Maximum treatment duration for anti–PD-1 immunotherapies specified?	Proportion of patients remaining on treatment at 2 years (K-M data)
RELATIVITY-047 trial	No	Nivolumab-relatlimab: [redacted]% Nivolumab: [redacted]%
CheckMate-067 trial[44]	No	Nivolumab+ipilimumab: [redacted]% Nivolumab: [redacted]%
KEYNOTE-006 trial[49]	Pembrolizumab* (2 years)	-

PD-1=programmed death-1
*A small number (n=18) of patients received second-course/subsequent pembrolizumab after completing a 2 year treatment course of pembrolizumab
Source: Company model, CheckMate 067 trial,[44] KEYNOTE-006 trial[49]

The company modelled TTD for patients treated with nivolumab-relatlimab and nivolumab (pembrolizumab) by fitting distributions to RELATIVITY-047 trial data.

The company modelled TTD for patients treated with nivolumab+ipilimumab using CheckMate 067 trial[44] nivolumab+ipilimumab K-M TTD data; these trial data are available for a period of [redacted] years. From this point on, patients are not treated with ipilimumab (as ipilimumab is limited to four treatment cycles), however, [redacted]% of patients are still being treated with nivolumab. With the removal of the 2-year treatment stopping rule, [redacted]% of patients continue to be treated with nivolumab until disease progression or death. This means that all the patients who receive treatment with nivolumab at [redacted] years continue to receive nivolumab treatment until disease progression or death. As TTD for patients treated with nivolumab-relatlimab, nivolumab and pembrolizumab are modelled using distributions rather than K-M data, over time, the proportions of patients on these treatments decline. For example, [redacted]% of patients treated with nivolumab monotherapy are on treatment at [redacted] and by Year 15 this proportion has fallen to [redacted]%.

The company's different approaches to modelling TTD only become an issue when the 2-year treatment stopping rule is removed. Therefore, when removing the 2-year treatment stopping rule, the EAG has modelled treatment with nivolumab+ipilimumab using the CheckMate 067 trial[44] nivolumab+ipilimumab TTD K-M data for [redacted] years and then applied nivolumab monotherapy TTD hazards (as applied in the company base case) for the remaining 35 years.

6.6 *Subsequent systemic treatments*

The per patient cost of subsequent treatments presented in CS, Table 65 represent a large proportion of total costs when weighted by the proportion of patients initiating subsequent treatment, particularly for the IO monotherapies (nivolumab-relatlimab: [redacted]%, nivolumab: [redacted]%, nivolumab+ipilimumab: [redacted]%, pembrolizumab: [redacted]%). Cost effectiveness results are therefore sensitive to changes in the assumptions or values used to calculate these costs. Subsequent

systemic treatment costs comprise three components: the proportion of patients who initiate subsequent systemic treatment, the distribution of subsequent systemic treatments and the mean time on subsequent systemic treatments.

6.6.1 Proportion of patients initiating subsequent systemic treatment

The proportions of patients modelled to receive subsequent systemic treatments are provided in

Table 46.

The company did not use RELATIVITY-047 trial data to model subsequent treatments as follow-up data were too short to provide reliable estimates (median follow-up= [redacted] months). Instead, in line with the NICE Melanoma HEMR committee preferred approach, the company used CheckMate 067 trial (5-year OS follow-up)[5] data to estimate the proportions of patients who received any subsequent treatments, including radiotherapy, surgery and investigational procedures. The EAG agrees that it was appropriate to use CheckMate 067 trial[5] subsequent treatment data; however, as the RELATIVITY-047 trial data show that [redacted] (CS, Table 16) and as the company model only includes systemic subsequent treatments, the EAG considers that CheckMate 067 trial[5] subsequent **systemic** treatment data should have been used to model subsequent systemic treatment for patients treated with nivolumab+ipilimumab and nivolumab (

Table 46).

For patients treated with nivolumab-relatlimab, the company has assumed that the proportion of patients receiving subsequent systemic treatment lies between the proportion receiving subsequent systemic treatment following nivolumab (59%) and the proportion receiving subsequent systemic treatment following nivolumab+ipilimumab (46%), i.e., [redacted]%. In the RELATIVITY-047 trial, the proportions of patients in both trial arms who received subsequent systemic treatments were similar (nivolumab-relatlimab: [redacted]%, nivolumab: [redacted]%). The EAG has therefore assumed that the proportions of patients treated with nivolumab-relatlimab and nivolumab who receive subsequent systemic treatments are equal.

The company, in line with the NICE Melanoma HEMR committee preferred approach, assumed that the proportion of patients receiving subsequent treatment following pembrolizumab was the same as the proportion of patients receiving subsequent treatment following nivolumab (CheckMate 067 trial[5] subsequent systemic treatment data). The EAG considers that this is a reasonable approach.

Table 46 Proportions of patients initiating subsequent systemic treatment

First-line treatment	Patients receiving subsequent treatment	Patients receiving subsequent systemic treatment		
	Company model	RELATIVITY-047 trial	CheckMate 067 trial	EAG preferred
Nivolumab-relatlimab	[redacted]%	[redacted]%	-	48%
Nivolumab	59%	[redacted]%	48%	48%
Nivolumab+ipilimumab	46%	-	35%	35%
Pembrolizumab	59%	-	-	48%

CS=company submission; EAG=External Assessment Group
Source: CS, Tables 57 and 58, CheckMate 067 trial[5]

6.6.2 Subsequent systemic treatment distributions and time on treatment

The company assumed that patients who received nivolumab-relatlimab (and initiated subsequent treatment) would not receive ipilimumab monotherapy as a subsequent systemic treatment (CS, Table 65). The rationale behind this assumption was that patients who received nivolumab-relatlimab would receive the same subsequent treatments as patients who had received nivolumab+ipilimumab (CS, p145). However, clinical advice to the EAG is that some patients who are treated with nivolumab-relatlimab in the first-line setting would receive ipilimumab monotherapy as a subsequent systemic treatment; these patients would be identified based on performance status and tolerability of prior treatment. The nivolumab-relatlimab safety profile is more similar to the nivolumab safety profile (CS, Table 19) than to the nivolumab+ipilimumab safety profile (CS, Table 23). The EAG has therefore assumed that the proportion of nivolumab-relatlimab patients who receive subsequent ipilimumab monotherapy is the same as the proportion of nivolumab (and pembrolizumab) patients who receive ipilimumab monotherapy (61.48% [CS, Table 61]). The EAG has made the same assumption in relation to time on treatment.

Table 47 Company and EAG modelled subsequent systemic treatments and time on treatment

	Nivolumab-relatlimab	Nivolumab	Nivolumab+ ipilimumab	Pembrolizumab
Company				
Ipilimumab	-	61.48%	-	61.48%
Dabrafenib+trametinib	19.26%	19.26%	19.26%	19.26%
Encorafenib+binimetinib	19.26%	19.26%	19.26%	19.26%
Clinical trials	61.48%	-	61.48%	-
Mean time on treatment	*8.81 months*	*7.77 months*	*8.81 months*	*7.77 months*
EAG				
Ipilimumab	61.48%	61.48%	-	61.48%
Dabrafenib+trametinib	19.26%	19.26%	19.26%	19.26%
Encorafenib+binimetinib	19.26%	19.26%	19.26%	19.26%
Clinical trials	-	-	61.48%	-
Mean time on treatment	*7.77 months*	*7.77 months*	*8.81 months*	*7.77 months*

CS=company submission; EAG=External Assessment Group
Source: CS, Table 61

The differences in subsequent treatment acquisition costs due to EAG changes are presented in Table 48.

Table 48 Subsequent systemic treatment acquisition costs using PAS prices for all company assets (weighted by proportion of patients who receive subsequent systemic treatment)

First-line treatment	Subsequent systemic treatment acquisition costs	
	Company model	EAG preferred
Nivolumab-relatlimab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab+ipilimumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]

EAG=External Assessment Group

6.7 *Adverse event costs and disutilities for nivolumab+ipilimumab*

The company has assumed that the same AE costs and disutilities should be applied to each cycle for the duration that patients receive IO therapies. The EAG has some concerns about this approach as AEs tend to occur more frequently at the start of treatment; however, clinical advice to the company and the EAG was that the company's approach was appropriate. However, the company has applied the same AE costs and disutilities associated with nivolumab+ipilimumab (incidence rates sourced from CheckMate 067 trial 60-month follow-up data) irrespective of whether the patient is receiving nivolumab+ipilimumab (four treatment cycles) or nivolumab monotherapy (until disease progression or death). The EAG considers that whilst there may be some residual adverse effects from having been treated with

ipilimumab, it is more appropriate to only apply the AE costs and disutilities associated with nivolumab monotherapy once treatment with ipilimumab has stopped.

6.8 *Application of utility values to long-term survival population*

The company has applied health state-specific utility values, which are lower than general population utility values, to patients in the PF and PD health states. In the company model, a proportion of patients have a very low or zero risk of disease progression or death from around 4-10 years after starting treatment until death. The company's approach means there is a residual negative effect on patient HRQoL, i.e., patient HRQoL is lower than general population HRQoL even when the patient is no longer at risk of disease progression and mortality hazards match general population mortality hazards.

The EAG considers that it is likely that QALYs are underestimated in the company base case analysis due to the assumption that patients who experience long-term survival will continue to have the same HRQoL as patients who do not experience long-term survival. The EAG has carried out an exploratory analysis using general population utility values to model HRQoL for patients in the PF and PD heath states from the time point when mortality risk equals general population mortality risk.

6.9 *EAG revision to company IV administration costs*

The company used two IV administration costs in the model for each IO therapy. The cost associated with delivering complex chemotherapy (NHS Reference Costs SB14Z [weighted average]) was used to cost the administration of the first dose of nivolumab-relatlimab, nivolumab, pembrolizumab and the first four doses of nivolumab+ipilimumab. The cost of administering subsequent elements of chemotherapy (NHS Reference Costs SB15Z [weighted average]) was used to cost the administration of all subsequent doses of all treatments.

The EAG considers that the company base case IV administration costs are higher than the costs that would be incurred in the NHS. The EAG has therefore replaced SB14Z (weighted average) with SB12Z (outpatient) for all doses of nivolumab-relatlimab, nivolumab, and pembrolizumab and has used the SB14Z (outpatient) cost to estimate the administration cost of the first four doses of nivolumab+ipilimumab. The EAG considers that these costs more accurately reflect the infusion times of modelled IO therapies than the costs used by the company. The EAG model IV administration costs are presented in

Table 49.

Table 49 IV administration costs applied in the model

Company model costs		EAG costs		
IV administration costs*	**Description**	**First line treatment**	**IV administration cost**	**Description**
£526.52	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance [SB14Z] (weighted average of settings)	Nivolumab-relatlimab	£281.11	Deliver simple parenteral chemotherapy at first attendance [SB12Z] (outpatient setting)
		Nivolumab		
		Pembrolizumab		
£470.62	Deliver subsequent elements of a chemotherapy cycle [SB15Z] (weighted average of settings)	Nivolumab+ ipilimumab	£342.66	Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance [SB14Z] (outpatient setting)

*The company applied the SB14Z cost for the first 3 doses of nivolumab+ipilimumab and for the first dose of all other treatments. The SB15Z cost was applied to all treatment doses thereafter
EAG=External Assessment Group; IV=intravenous
Source: CS Table 49, NHS Reference Costs 2020/21[73]

6.10 *Impact on the company base results of EAG revisions*

The EAG has made the following revisions to the company base case:

R1) RELATIVITY-047 trial PFS (investigator-assessed)

R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS

R3) Constant HRs from the company adjusted ITC for nivolumab+ipilimumab

R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)

R5) TTD constraint (≤ PFS) removed

R6a) 2 year stopping rules for IO therapies removed

R6b) 2 year stopping rule removed; plus nivolumab+ipilimumab K-M data used up to [redacted] years and nivolumab TTD hazards applied thereafter

R7) Alternative subsequent treatment cost calculations

R8) EAG change to IV administration costs

R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD

R10) General population utility from point of background mortality hazard

R11) EAG combined exploratory analysis

Details of how the EAG revised the company model are presented in Appendix 7 (Section 8.7) of this EAG report. EAG pairwise deterministic and probabilistic cost effectiveness results (nivolumab-relatlimab versus each comparator) are presented in Table 50 to

Table 55. Fully incremental analyses of probabilistic cost effectiveness results for the company base case (company addendum) and the EAG alternative scenarios (B) are presented in Section 6.11. All cost effectiveness results have been generated using PAS prices for company assets and list prices for all other drugs.

Table 50 Deterministic results (nivolumab-relatlimab vs nivolumab), PAS prices for all company assets

Scenario/EAG revisions*	Nivolumab-relatlimab		Nivolumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,426**
R1) RELATIVITY-047 trial PFS (investigator-assessed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,049
R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS							
R3) Constant HRs from the company adjusted ITC for nivolumab+ipilimumab							
R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)							
R5) TTD constraint (≤ PFS) removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,848
R6a) 2 year stopping rules for IO therapies removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,876
R6b) 2 year stopping rule removed; plus nivolumab+ipilimumab K-M data used up to [redacted] years and nivolumab TTD hazards applied thereafter							
R7) Alternative subsequent treatment cost calculations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,038
R8) EAG change to IV administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,725
B. EAG alternative scenario (R1, R5, R6a, R7, R8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£44,404**
C. EAG exploratory analyses							
R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD							
R10) General population utility from point of background mortality hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,351
R11) EAG combined exploratory analysis (R1, R4-R6a, R7-R9)							

*Grey text=irrelevant revision

AE=adverse event; CS=company base case; EAG=External Assessment Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; IO=immune-oncology; ITCs=indirect treatment comparisons; IV=intravenous; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 51 Probabilistic results (nivolumab-relatlimab vs nivolumab), PAS prices for all company assets

Scenario	Nivolumab-relatlimab		Nivolumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£18,107**
A2. Company base case (NMA parameter sampling error corrected)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£18,731**
B. EAG alternative scenario (R1, R5, R6a, R7, R8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,931**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Table 52 Deterministic results (nivolumab-relatlimab vs nivolumab+ipilimumab), PAS prices for all company assets

Scenario/EAG revisions*	Nivolumab-relatlimab		Nivolumab+ipilimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**
R1) RELATIVITY-047 trial PFS (investigator-assessed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS							
R3) Constant HRs from company adjusted ITC for nivolumab+ipilimumab[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R5) TTD constraint (≤ PFS) removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R6a) 2 year stopping rules for IO therapies removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R6b) 2 year stopping rule removed; plus nivolumab+ipilimumab K-M data used up to [redacted] years and nivolumab TTD hazards applied thereafter	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,936
R7) Alternative subsequent treatment cost calculations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,319
R8) EAG change to IV administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
B. EAG alternative scenario (R1, R3-R5, R6b-R8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£118,253**
C. EAG exploratory analyses							
R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R10) General population utility from point of background mortality hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R11) EAG combined exploratory analysis (R1, R4-R6a, R7-R9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,974,310

*Grey text=irrelevant revision

[a] PFS constant HRs from the company adjusted ITC for investigator-assessed PFS

AE=adverse event; CS=company base case; EAG=External Assessment Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; IO=immune-oncology; ITCs=indirect treatment comparisons; IV=intravenous; K-M=Kaplan-Meier; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 53 Probabilistic results (nivolumab-relatlimab vs nivolumab+ipilimumab), PAS prices for all company assets

Scenario	Nivolumab-relatlimab		Nivolumab+ ipilimumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**
A2. Company base case (NMA parameter sampling error corrected)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**
B. EAG alternative scenario (R1, R3-R5, R6b-R8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£113,277**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Table 54 Deterministic results (nivolumab-relatlimab vs pembrolizumab), PAS prices for all company assets

Scenario/EAG revisions*	Nivolumab-relatlimab		Pembrolizumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**
R1) RELATIVITY-047 trial PFS (investigator-assessed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R3) Constant HRs from company's adjusted ITC for							
R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)							
R5) TTD constraint (≤ PFS) removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R6a) 2 year stopping rules for IO therapies removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R6b) 2 year stopping rule removed; plus nivolumab+ipilimumab K-M data used up to [redacted] years and nivolumab TTD hazards applied							
R7) Alternative subsequent treatment cost calculations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R8) EAG change to IV administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
B. EAG alternative scenario (R1-R2, R5, R6a, R7-R8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**
C. EAG exploratory analyses							
R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD							
R10) General population utility from point of background mortality hazards	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NIV-REL dominates
R11) EAG combined exploratory analysis (R1, R4-R6a, R7-R9)							

*Grey text=irrelevant revision

AE=adverse event; CS=company base case; EAG=External Assessment Group; HR=hazard ratio; ICER=incremental cost effectiveness ratio; IO=immune-oncology; ITCs=indirect treatment comparisons; IV=intravenous; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Table 55 Probabilistic results (nivolumab-relatlimab vs pembrolizumab), PAS prices for all company assets

Scenario	Nivolumab-relatlimab		Pembrolizumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1. Company base case (addendum)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**
A2. Company base case (NMA parameter sampling error corrected)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**
B. EAG alternative scenario (R1-R2, R5, R6a, R7-R8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**NIV-REL dominates**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life year

6.11 *EAG fully incremental results*

Table 56 Company base case (A1) probabilistic results, PAS prices for all company assets

Treatment	Total costs	Total QALYs	ICER per QALY gained
Nivolumab	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	£18,107
Nivolumab+ipilimumab	[redacted]	[redacted]	Strictly dominated
Pembrolizumab	[redacted]	[redacted]	Strictly dominated

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Table 57 Company base case (A2) probabilistic results (NMA parameter sampling error corrected), PAS prices for all company assets

Treatment	Total costs	Total QALYs	ICER per QALY gained
Nivolumab	[redacted]	[redacted]	-
Nivolumab-relatlimab	[redacted]	[redacted]	£18,731
Nivolumab+ipilimumab	[redacted]	[redacted]	Strictly dominated
Pembrolizumab	[redacted]	[redacted]	Strictly dominated

ICER=incremental cost effectiveness ratio; NMA=network meta-analysis; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Table 58 EAG alternative scenario (B) probabilistic results, PAS prices for all company assets

Treatment	Total costs	Total QALYs	ICER per QALY gained
Nivolumab	[redacted]	[redacted]	-
Nivolumab+ipilimumab	[redacted]	[redacted]	£19,413
Nivolumab-relatlimab	[redacted]	[redacted]	£113,277
Pembrolizumab	[redacted]	[redacted]	Strictly Dominated

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

6.11.1 Disease severity modifier

The EAG corrected the error in the company's calculation of general population QALYs and recalculated the disease severity modifier. This correction did not change the decision not to apply a disease severity modifier. The EAG recalculated the disease severity modifier using EAG preferred scenario results; the modifier remained at 1.

6.12 *Cost effectiveness conclusions*

The company model relies heavily on RELATIVITY-047 trial and CheckMate 067 trial[5,44] data. The EAG considers that the RELATIVITY-047 trial provides robust clinical effectiveness evidence for the comparison of nivolumab-relatlimab versus nivolumab for patients for whom treatment with an IO combination therapy is suitable. Indirect evidence is available from the company adjusted ITCs for the comparison of nivolumab-relatlimab versus nivolumab+ipilimumab. However, the relative benefit of nivolumab-relatlimab versus nivolumab+ipilimumab remains uncertain due to the immaturity of RELATIVITY-047 trial data. The EAG considers that there is no robust evidence for the comparison of nivolumab-relatlimab versus pembrolizumab; the EAG has set pembrolizumab PFS/OS equal to nivolumab PFS/OS (RELATIVITY-047 trial).

Nivolumab monotherapy

The company base case probabilistic (deterministic) ICER for the comparison of nivolumab-relatlimab versus nivolumab is £18,731 (£20,426) per QALY gained. In contrast, the EAG alternative probabilistic (deterministic) ICER is £45,931 (£44,404) per QALY gained. The EAG revisions that had the biggest impact on cost effectiveness results were removal of the 2-year treatment stopping rule and alternative costing of subsequent systemic therapies.

Nivolumab+ipilimumab

For the comparison of nivolumab-relatlimab versus nivolumab+ipilimumab, company base case probabilistic and deterministic results show that nivolumab-relatlimab dominates nivolumab+ipilimumab. In contrast, the EAG alternative probabilistic (deterministic) ICER is £113,277 (£118,253) per QALY gained. The EAG revisions that had the biggest impact on cost effectiveness results were removal of the 2-year treatment stopping rule (which the EAG considers also involved more appropriate modelling of TTD and AEs for patients treated with nivolumab+ipilimumab) and alternative costing of subsequent systemic therapies.

Pembrolizumab

For the comparison of nivolumab-relatlimab versus pembrolizumab, company base case and EAG alternative probabilistic and deterministic results show that nivolumab-relatlimab dominates pembrolizumab.

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8. APPENDICES

8.1 *Appendix 1: Trials identified and included in the NMAs*

Table 59 Baseline patient characteristics of trials included in the company and EAG NMAs

Trial (population)	Treatment	N	Age, years, Median (range)	Male, n (%)	ECOG PS score, n (%)[a]			AJCC Stage, n (%)[b]		Metastasis stage, n (%)[c,d,e]				History of brain metastases, n (%)
					0	1	≥2	III	IV	M0	M1a	M1b	M1c	
RELATIVITY-047 (ITT population)	Nivolumab-relatlimab	355	63 (20 to 94)	210 (59.2)	236 (66.5)	119 (33.5)	0 (0)	[redacted]	[redacted]	35 (9.9)	77 (21.7)	85 (23.9)	151 (42.5)	[redacted]
	Nivolumab	359	62 (21 to 90)	206 (57.4)	242 (67.4)	117 (32.6)	0 (0)	[redacted]	[redacted]	23 (6.4)	107 (29.8)	88 (24.5)	127 (35.4)	[redacted]
CheckMate 067 (ITT population)	Ipilimumab	315	62 (18 to 89)	202 (64.1)	224 (71.1)	91 (28.9)	0 (0)	22 (7)	293 (93)	132 (41.9)			189 (60)	15 (4.8)
	Nivolumab+ ipilimumab	314	61 (18 to 88)	206 (65.6)	230 (73.2)	83 (26.4)	0 (0)	17 (5.4)	297 (94.6)	133 (42.4)			185 (58.9)	11 (3.5)
	Nivolumab	316	60 (25 to 90)	202 (63.9)	238 (75.3)	77 (24.4)	1 (0.3)	25 (7.9)	291 (92.1)	132 (41.8)			185 (58.5)	8 (2.5)
CheckMate 069 (ITT population)	Ipilimumab	47	67 (31 to 80)	32 (68.1)	37 (78.7)	10 (21.3)	0 (0)	9 (19.1)	38 (80.9)	5 (10.6)	8 (17.0)	12 (25.5)	21 (44.7)	0 (0)
	Nivolumab+ ipilimumab	95	64 (27 to 87)	63 (66.3)	79 (83.2)	14 (14.7)	2 (2.1)	10 (10.5)	85 (89.5)	8 (8.4)	15 (15.8)	27 (28.4)	44 (46.3)	4 (4.2)
KEYNOTE-006 (ITT population)[f]	Ipilimumab	278	62 (18 to 88)	162 (58.3)	188 (67.6)	90 (32.4)	0 (0)	NR	NR	14 (5.0)	30 (10.8)	52 (18.7)	177 (63.7)	28 (10.1)
	Pembrolizumab Q2W/Q3W arms combined	556	62 (18 to 89)	335 (60.3)	385 (69.2)	171 (30.8)	0 (0)	NR	NR	18 (3.2)	55 (9.9)	105 (18.9)	368 (66.2)	50 (9.0)

[a] 1 patient (0.3%) with ECOG PS score not reported in the nivolumab+ipilimumab arm of the CheckMate 067 trial[17,34]
[b] 1 patient (0.3%) with unknown AJCC stage in the nivolumab arm of the RELATIVITY-047 trial[16]
[c] In the RELATIVITY-047 trial, 6 patients (1.7%) in the nivolumab-relatlimab arm and 11 patients (3.1%) in the nivolumab arm had baseline metastases stage M1d, a new designation added to the eighth edition of the AJCC melanoma staging system[50]. The CheckMate 067,[17,34] CheckMate 069[18] and KEYNOTE-006 trials[19] used an earlier edition of the AJCC melanoma staging system[79]
[d] Baseline metastases stage was not reported for 1 patient (1%) in the nivolumab+ipilimumab arm and for 1 (2%) patient in the ipilimumab arm of the CheckMate 069 trial
[e] 0 patients (1.8%) in the combined pembrolizumab arms and 5 patients (1.8%) with M1 metastasis stage in the KETNOTE-006 trial; further classification of the metastasis stage not reported.
[f] Outcome data were extracted for the treatment naïve (first-line) subgroup of the KEYNOTE-006 trial where possible (see Table X), baseline characteristics were available only for the ITT population
AJCC=American Joint Cancer Committee; EAG=External Assessment Group; ECOG=Eastern Cooperative Oncology Group; ITT=intention to treat; NMA=network meta-analysis; NR=not reported; PS=performance status; Q2W=every 2 weeks, Q3W=every 3 weeks
Source: CS, Table 10 and CS, Appendix D, Table 8; RELATIVITY-047 trial primary CSR, primary publications of the CheckMate 067,[17,34] CheckMate 069[18] and KEYNOTE-006 trials[19]

Table 60 Risk of bias assessment of the trials included in the company and EAG NMAs

Trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
RELATIVITY-047	Low Stratified permuted block randomisation (TSAP Section 2.2)	Low IRT system used (TSAP Section 2.2)	Low Sponsor, subjects, investigator and site staff were blinded to the study drug administered (TSAP Section 2.23)	Low Sponsor, subjects, investigator and site staff were blinded to the study drug administered (TSAP Section 2.23)	Low Study attrition reported and ITT approach used	Low All endpoints pre-specified in the protocol reported in the CS and CSR	Low No other bias detected
CheckMate 067	Low Stratified permuted block randomisation (protocol Section 4.2)	Low IVRS used (protocol Section 4.2)	Low Sponsor, subjects, investigator and site staff were blinded to the study drug administered (protocol Section 4.4)	Low Sponsor, subjects, investigator and site staff were blinded to the study drug administered (protocol Section 4.4)	Low Study attrition reported and ITT approach used	Low All endpoints pre-specified in the protocol reported in trial publications	Low No other bias detected
CheckMate 069	Low Stratified permuted block randomisation (protocol Section 4.2)	Low IVRS used (protocol Section 4.2)	Low Sponsor, subjects, investigator and site staff were blinded to the study drug administered (protocol Section 4.4)	Low Sponsor, subjects, investigator and site staff were blinded to the study drug administered (protocol Section 4.4)	Low Study attrition reported and ITT approach used	Low All endpoints pre-specified in the protocol reported in trial publications	Low No other bias detected
KEYNOTE-006	Unclear Randomisation performed in IVRS system (protocol Section 3.2.5.6), no further details given	Low IVRS used (protocol Section 3.2.5.6)	High Open label trial	Low Outcome assessors blinded (i.e. statistical team and independent radiologists; Protocol Section 3.5.1)	Low Study attrition reported and ITT approach used	Low All endpoints pre-specified in the protocol reported in trial publications	Low No other bias detected

EAG=External Assessment Group; IRT=interactive response technology; ITT=intention to treat; IVRS=interactive voice response system; TSAP=trial statistical analysis plan
Source: CS, primary CSR[33] and CSR Addendum 02,[34] TSAP[35] and trial protocol of the RELATIVITY-047 trial,[32] publications of the CheckMate 067,[17] CheckMate 069[18] and KEYNOTE-006[19] trials (see Table 5 for references to trial publications)

8.2 *Appendix 2: Outcome data included in company and EAG NMAs*

Table 61 PFS and OS outcome data from the trials included in the company and EAG NMAs (constant HRs)

Trial	Comparison (n)	Follow-up	BICR-assessed PFS[a,b]		Investigator-assessed PFS[b]		OS[a,b]	
			HR (95% CI)	Source	HR (95% CI)	Source	HR (95% CI)	Source
RELATIVITY-047 (ITT population)	Nivolumab-relatlimab ([redacted]) vs nivolumab ([redacted])	Median [redacted] months	[redacted]	CS, Table 13	[redacted]	Clarification Question A5, Table 3	[redacted]	CS, Table 14
CheckMate 067 (ITT population)	Nivolumab+ipilimumab (n=314) vs nivolumab (n=316)	Minimum 90 months	NR (Investigator-assessed PFS only reported)		0.79 (0.65 to 0.97)	Hodi 2022[44]	0.84 (0.68 to 1.04)	Hodi 2022[44]
	Nivolumab+ipilimumab (n=314) vs ipilimumab (n=315)				0.42 (0.35 to 0.51)		0.53 (0.44 to 0.65)	
	Nivolumab (n=316) vs ipilimumab (n=315)				0.53 (0.44 to 0.64)		0.63 (0.52 to 0.77)	
CheckMate 069 (ITT population)	Nivolumab+ipilimumab (n=95) vs ipilimumab (n=47)	Median 26.6 months	NA (Investigator-assessed PFS only reported)		0.36 (0.22 to 0.56)	Hodi 2016[45]	0.74 (0.43 to 1.26)	Hodi 2016[45]
KEYNOTE-006 (treatment naïve [i.e., first-line] subgroup)	Pembrolizumab (combined groups, n=368) vs ipilimumab (n=181)	Median 57.7 months	NA (Investigator-assessed PFS only for updated analyses[49])		0.54 (0.44 to 0.67)	Robert 2019[49]	0.73 (0.57 to 0.92)	Robert 2019[49]

[a] Data included in NMAs conducted by the company. To estimate time-varying HRs, the company used PLD from the RELATIVITY-047 trial and digitized data from K-M curves in the Hodi 2022[44] publication of the CheckMate 067 trial, the Hodi 2016[45] publication of the CheckMate -067 trial and from the Robert 2019[49] publication of the KEYNOTE-006 trial
[b] Data included in NMAs conducted by the EAG
BICR=blinded independent central review; CI=confidence interval; EAG=External Assessment Group; HR=hazard ratio; ITT=intention to treat; NMA=network meta-analysis; NR=not reported; OS=overall survival; PFS=progression free survival; PLD=patient level data

Table 62 Safety outcome data from the trials included in the company and EAG NMAs[a]

Trial (population)	Treatment	N	Grade 3 to 4 AEs		Grade 3 to 4 TRAEs		Discontinuation due to AEs		Discontinuation due to TRAEs	
			n	Source (median follow-up)	n	Source (median follow-up)	n	Source (median follow-up)	n	Source (median follow-up)
RELATIVITY-047 (safety population)	Nivolumab-relatlimab	[redacted]	[redacted]	Clarification Question C3, Table 34 [redacted] months)	[redacted]	Clarification Question C3, Table 34 [redacted] months)	[redacted]	Clarification Question C3, Table 34 [redacted] months)	[redacted]	Clarification Question C3, Table 34 [redacted] months)
	Nivolumab	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
CheckMate 067 (safety population	Nivolumab+ Ipilimumab	313	215	Larkin 2015[17] (12.2 to 12.5 months)[c]	186	Wolchok 2022[43] (18.6 to 57.5 months)[c]	139	Wolchok 2022[43] (18.6 to 57.5 months)[c]	131	Wolchok 2022[43] (18.6 to 57.5 months)[c]
	Nivolumab	313	136		74		49		43	
	Ipilimumab	311	173		86		52		47	
CheckMate 069 (safety population)	Nivolumab+ Ipilimumab	95	NR	NA (TRAEs only reported)	51	Hodi 2016[45] (26.6 months)	NR	NA (TRAEs only reported)	46	Hodi 2016[45] (26.6 months)
	Ipilimumab	47	NR		9		NR		10	
KEYNOTE-006 (safety population)[b]	Pembrolizumab (combined groups)	555	NR	NA (TRAEs only reported)	96	Robert 2019[49] (57.7 months)	81	Robert 2019[49] (57.7 months)	55	Robert 2019[49] (57.7 months)
	Ipilimumab	256	NR		50		35		23	

[a] The EAG made corrections errors in the 'Summary of safety NMA data sources (Clarification response, question A12, Table 16) where numbers of events were inverted across treatment arms in the RELATIVITY-047 trial, the CheckMate 067 trial and the KEYNOTE-006 trial.
[b] Safety outcome data were not reported separately for the treatment naïve subgroup. Therefore, safety data include 262 patients (34%) who had received one line of previous systemic therapy for advanced disease.
[c] Median follow up ranges from ipilimumab arm to nivolumab+ipilimumab arm
AE=adverse events; EAG=External Assessment Group; NA=not applicable; NMA=network meta-analysis; NR=not reported; TRAE=treatment related adverse events

Table 63 ORR outcome data from the trials included in the EAG NMAs[a]

Trial	Treatment	N	ORR (n)	ORR (%)	Source	Assessment method	Median follow-up
RELATIVITY-047 (ITT population)	Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	CS, Table 15	BICR	[redacted] months
	Nivolumab	[redacted]	[redacted]	[redacted]			
CheckMate 067 (ITT population)	Nivolumab+ipilimumab	314	183	58.3	Larkin 2019[5]	Investigator	18.6 (ipilimumab arm) to 54.6 months (nivolumab+ ipilimumab arm)
	Nivolumab	316	141	44.6			
	Ipilimumab	315	60	19.0			
CheckMate 069 (ITT population)	Nivolumab+ipilimumab	95	56	58.9	Hodi 2016[45]	Investigator	26.6 months
	Ipilimumab	47	5	10.6			
KEYNOTE-006 (treatment naïve [i.e., first-line] subgroup)	Pembrolizumab (combined groups)	368	170	46.2	Robert 2019[49]	Investigator	57.7 months
	Ipilimumab	181	31	17.1			

[a] Summary data included only in EAG NMAs, the company did not conduct ORR NMAs
BICR=blinded independent central review; EAG=External Assessment Group; ITT=intention to treat; NMA=network meta-analysis; ORR=objective response rate

8.3 *Appendix 3: Statistical code for EAG NMAs*

Fixed effect NMAs of contrast-based time-to-event data (PFS and OS)

```
###     Install and run multinma to conduct Bayesian network meta-analysis        ###

if (!require("multinma")) install.package("multinma")
library("multinma")
options(mc.cores = parallel::detectCores())

###     Load datasets ###
PFS_BICR <- read.csv("PFS BICR.csv")
PFS_INV <- read.csv("PFS INV.csv")
OS <- read.csv("OS.csv")

###     Setting up networks ###

PFS_BICR_net <- set_agd_contrast(PFS_BICR,
                    study = study_c,
                    trt = trt_c,
                    y = logHR,
                    se = selogHR,
                    sample_size = n_total,
                    trt_ref = "Nivolumab-relatlimab ")
plot(PFS_BICR_net , weight_edges = TRUE, weight_nodes = TRUE)

PFS_INV_net <-                  set_agd_contrast(PFS_INV,
                    study = study_c,
                    trt = trt_c,
                    y = logHR,
                    se = selogHR,
                    sample_size = n_total,
                    trt_ref = "Nivolumab-relatlimab ")
plot(PFS_INV_net , weight_edges = TRUE, weight_nodes = TRUE)

OS_net <-               set_agd_contrast(OS,
                    study = study_c,
                    trt = trt_c,
                    y = logHR,
                    se = selogHR,
                    sample_size = n_total,
                    trt_ref = "Nivolumab-relatlimab ")
plot(OS_net , weight_edges = TRUE, weight_nodes = TRUE)


###     Fixed effects NMA               ###

FE_PFS_BICR <-      nma(PFS_BICR_net,
                        trt_effects = "fixed",
                        consistency = "consistency",
                        chains = 3,
                        iter = 2e5,
                        warmup = 1e5,
                        prior_intercept = normal(scale = 100),
                        prior_trt = normal(scale = 100))
```

```
FE_PFS_INV <-       nma(PFS_INV_net,
                    trt_effects = "fixed",
                    consistency = "consistency",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))

FE_OS <-            nma(OS_net,
                    trt_effects = "fixed",
                    consistency = "consistency",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))


### Generate all pairwise contrasts between treatments     ###
(FE_all_PFS_BICR <- relative_effects(FE_PFS_BICR, all_contrasts = TRUE))
(FE_all_PFS_INV <- relative_effects(FE_PFS_INV, all_contrasts = TRUE))
(FE_all_OS <- relative_effects(FE_OS, all_contrasts = TRUE))


### Inconsistency model (unrelated mean effects model)    ###
### Example code for investigator assessed PFS  ###

FE_PFS_INV_inc <-   nma(PFS_INV_net,
                    trt_effects = "fixed",
                        consistency = "ume",
                        chains = 3,
                        iter = 2e5,
                        warmup = 1e5,
                        control = list(max_treedepth = 15),
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))

###     Show results   ###

FE_PFS_INV_inc


###     Model fit statistics for consistency and inconsistency models          ####

(dic_FE_PFS_INV <- dic(FE_PFS_INV))
(dic_FE_PFS_INV_inc <- dic(FE_PFS_INV_inc))
```

Fixed and random effects NMAs of arm-based binary data (ORR and safety outcomes)

```
###     Load datasets ###

ORR <- read.csv("ORR.csv")
AE_G34 <- read.csv("Grade 34 AEs.csv")
TRAE_G34 <- read.csv("Grade 34 TRAEs.csv")
AE_disc <- read.csv("Disc AEs.csv")
TRAE_disc <- read.csv("Disc TRAEs.csv")

###     Setting up networks ###

ORR_network <- set_agd_arm(ORR,
                  study = study_c,
                  trt = trt_c,
                  r=r,
                  n=n,
                  trt_ref = "Nivolumab-relatlimab ")
plot(ORR_network , weight_edges = TRUE, weight_nodes = TRUE)

AE_G34_network <- set_agd_arm(AE_G34,
                  study = study_c,
                  trt = trt_c,
                  r=r,
                  n=n,
                  trt_ref = "Nivolumab-relatlimab ")
plot(AE_G34_network , weight_edges = TRUE, weight_nodes = TRUE)

TRAE_G34_network <- set_agd_arm(TRAE_G34,
                  study = study_c,
                  trt = trt_c,
                  r=r,
                  n=n,
                  trt_ref = "Nivolumab-relatlimab ")
plot(TRAE_G34_network , weight_edges = TRUE, weight_nodes = TRUE)

AE_DISC_network <- set_agd_arm(AE_disc,
                  study = study_c,
                  trt = trt_c,
                  r=r,
                  n=n,
                  trt_ref = "Nivolumab-relatlimab ")
plot(AE_DISC_network , weight_edges = TRUE, weight_nodes = TRUE)

TRAE_DISC_network <- set_agd_arm(TRAE_disc,
                  study = study_c,
                  trt = trt_c,
                  r=r,
                  n=n,
                  trt_ref = "Nivolumab-relatlimab ")
plot(TRAE_DISC_network , weight_edges = TRUE, weight_nodes = TRUE)


###     Fixed effects NMA               ###
```

```
FE_ORR        <-    nma(ORR_network,
                    trt_effects = "fixed",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))

FE_AE_G34     <-    nma(AE_G34_network,
                    trt_effects = "fixed",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))

FE_TRAE_G34        <-    nma(TRAE_G34_network,
                    trt_effects = "fixed",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))

FE_AE_DISC    <-    nma(AE_DISC_network,
                    trt_effects = "fixed",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))

FE_TRAE_DISC       <-    nma(TRAE_DISC_network,
                    trt_effects = "fixed",
                    consistency = "consistency",
                    link="logit",
                    chains = 3,
                    iter = 2e5,
                    warmup = 1e5,
                    prior_intercept = normal(scale = 100),
                    prior_trt = normal(scale = 100))

### Generate all pairwise contrasts between treatments     ###

(FE_all_ORR <- relative_effects(FE_ORR, all_contrasts = TRUE))
(FE_all_AE_G34 <- relative_effects(FE_AE_G34, all_contrasts = TRUE))
```

```
(FE_all_TRAE_G34 <- relative_effects(FE_TRAE_G34, all_contrasts = TRUE))
(FE_all_AE_DISC <- relative_effects(FE_AE_DISC, all_contrasts = TRUE))
(FE_all_TRAE_DISC <- relative_effects(FE_TRAE_DISC, all_contrasts = TRUE))
```

8.4 *Appendix 4: Results of additional EAG NMAs*

Table 64 shows results of EAG NMAs of ORR and safety outcomes. Results of company and EAG NMAs of safety outcomes are discussed in Section 3.7.4. Results of the EAG ORR NMA show no statistically significant difference for the comparisons of nivolumab-relatlimab versus nivolumab+ipilimumab, versus pembrolizumab or versus nivolumab. However, it should be noted that data from BICR-assessed ORR and investigator-assessed ORR are combined in the EAG NMA (see Appendix 2, Section 8.2, Table 63) . EAG concerns regarding the combination of data from BICR-assessed PFS and investigator-assessed PFS are discussed in Section 3.7.1.

Table 64 EAG NMA results: ORR and safety outcomes

Comparison	OR (95% CrI)				
	ORR[a]	Grade 3 to 4 AEs[b]	Grade 3 to 4 TRAEs[b]	Discontinuation due to AEs[b]	Discontinuation due to TRAEs[b]
Nivolumab-relatlimab vs nivolumab+ipilimumab	0.84 (0.55 to 1.31)	0.49 (0.31 to 0.76)	**0.43 (0.25 to 0.73)**	**0.36 (0.21 to 0.63)**	**0.49 (0.27 to 0.90)**
Nivolumab-relatlimab vs nivolumab	1.52 (1.13 to 2.08)	**1.39 (1.03 to 1.88)**	**2.08 (1.39 to 3.13)**	**1.60 (1.09 to 2.34)**	**2.20 (1.40 to 3.53)**
Nivolumab-relatlimab vs pembrolizumab	1.32 (0.70 to 2.51)	NE	**1.99 (1.03 to 3.86)**	1.36 (0.66 to 2.77)	1.73 (0.76 to 3.90)
Nivolumab-relatlimab vs ipilimumab	**5.58 (3.53 to 8.94)**	0.85 (0.55 to 1.32)	**1.72 (1.01 to 2.94)**	1.48 (0.84 to 2.61)	**1.95 (1.03 to 3.71)**
Nivolumab+ipilimumab vs nivolumab	**1.80 (1.32 to 2.46)**	**2.86 (2.08 to 3.97)**	**4.85 (3.46 to 6.82)**	**4.35 (3.00 to 6.42)**	**4.53 (3.10 to 6.75)**
Nivolumab+ipilimumab vs pembrolizumab	1.57 (0.90 to 2.72)	NE	**4.62 (2.83 to 7.54)**	**3.71 (2.12 to 6.55)**	**3.56 (1.90 to 6.55)**
Nivolumab+ipilimumab vs ipilimumab	**6.55 (4.71 to 9.30)**	**1.75 (1.26 to 2.44)**	**4.01 (2.94 to 5.47)**	**4.06 (2.80 to 5.87)**	**3.97 (2.83 to 5.70)**
Pembrolizumab vs nivolumab	1.15 (0.66 to 2.03)	NE	1.05 (0.63 to 1.77)	1.17 (0.64 to 2.16)	1.28 (0.66 to 2.53)
Nivolumab vs ipilimumab	**3.67 (2.56 to 5.21)**	**0.61 (0.44 to 0.84)**	0.83 (0.58 to 1.17)	0.92 (0.61 to 1.42)	0.88 (0.57 to 1.35)
Pembrolizumab vs ipilimumab	**4.22 (2.75 to 6.55)**	NE	0.86 (0.59 to 1.27)	1.08 (0.71 to 1.68)	1.13 (0.68 to 1.92)

[a] OR>1 favours the first treatment in the comparison over the second treatment for ORR. 95% CrIs that do not cross 1 (i.e., which are statistically significant) for results highlighted in **bold**
[b] OR<1 favours the first treatment in the comparison over the second treatment for safety outcomes. 95% CrIs that do not cross 1 (i.e., which are statistically significant) for results highlighted in **bold**
[c] not estimable for comparisons vs pembrolizumab as Grade 3 to 4 AEs were not reported for the KEYNOTE-006 trial
AEs=adverse events; CrI=credible intervals; EAG=External Assessment Group; NE=not estimable; NMA=network meta-analysis; OR=odds ratio; ORR=objective response rate; TRAEs=treatment related adverse events
Source: EAG analysis using statistical code in Appendix 3 (Section 8.3 above) applied to the data in Appendix 2 (Section 8.2, Table 62 and Table 63) of this EAG report

8.5 *Appendix 5: EAG assessment of inconsistency in the NMAs*

The EAG assessed the AG assessed inconsistency by applying an unrelated mean effects model[56] and by comparing model fit statistics and results of this inconsistency model with the results of the EAG NMAs presented in Table 20 and Table 64) which assume consistency.

Inconsistency models such as the unrelated mean effects model[56] are more complex than NMA models which assume consistency. Therefore, due to the small number of trials included in the network and instability of random-effects NMA results (Section 3.7.3, Table 17), fixed-effect inconsistency models only were applied.

Model fit statistics of fixed-effect EAG NMA models assuming consistency and inconsistency are presented in Table 65.

Table 65 Model fit statistics for EAG fixed-effects NMA consistency and inconsistency models

Outcome	Model[a]	Posterior mean residual deviance	Number of data points	pD	DIC
BICR / investigator-assessed PFS	Consistency	4.4	5	4	8.4
	Inconsistency	5	5	5	10
Investigator-assessed PFS	Consistency	4.5	5	4	8.5
	Inconsistency	5	5	5	10
OS	Consistency	5.5	5	4	9.5
	Inconsistency	5	5	5	10
ORR	Consistency	9.9	9	8	17.8
	Inconsistency	9.9	9	7.9	17.8
Grade 3-4 AEs	Consistency	5	5	5	10
	Inconsistency	5	5	5	10
Grade 3-4 TRAEs	Consistency	8.3	9	8	16.3
	Inconsistency	8.3	9	8	16.4
Discontinuation due to AEs	Consistency	7	7	7	14
	Inconsistency	7	7	7	14
Discontinuation due to TRAEs	Consistency	8.2	9	8	16.2
	Inconsistency	8.2	9	8	16.2

[a] Unrelated mean effects model[56] applied to assess inconsistency
AEs=adverse events; BICR=blinded independent central review; EAG=External Assessment Group; DIC=deviance information criterion; NMA=network meta-analysis; ORR=objective response rate; OS=overall survival; pD=effective number of model parameters; PFS=progression-free survival; TRAEs=treatment related adverse events
Source: EAG analysis using statistical code in EAG report Appendix 3 (Section 8.3) applied to the data in EAG report Appendix 2 (Section 8.2, Table 61)

Model fit statistics demonstrate that consistency models seem to provide a better fit (lower posterior mean residual deviance and DIC statistic) or the same level of model fit (equal posterior mean residual deviance and DIC statistic) compared to inconsistency models. EAG fixed-effects NMA results from the unrelated mean effects model (Table 66 and Table 67) were identical or very similar to the results of the AG fixed-effects PFS NMA results assuming

consistency (Table 20 and Table 64) and conclusions are unchanged for the comparisons of nivolumab-relatlimab versus nivolumab+ipilimumab, nivolumab and pembrolizumab. Therefore, the EAG is satisfied that no important inconsistency is present in the NMAs.

Table 66 EAG fixed-effect constant HR NMA results: PFS (BICR- and investigator-assessed) and OS

Comparison[a]	HR (95% CrI)		
	BICR / investigator-assessed PFS[b]	Investigator-assessed PFS[c]	OS
Nivolumab-relatlimab vs nivolumab+ipilimumab	1.03 (0.78 to 1.36)	1.12 (0.84 to 1.48)	0.97 (0.71 to 1.31)
Nivolumab-relatlimab vs nivolumab	**0.81 (0.67 to 0.98)**	0.88 (0.73 to 1.06)	0.82 (0.66 to 1.02)
Nivolumab-relatlimab vs pembrolizumab	0.79 (0.57 to 1.13)	0.87 (0.62 to 1.22)	0.70 (0.49 to 1.03)
Nivolumab-relatlimab vs ipilimumab	**0.43 (0.33 to 0.56)**	**0.47 (0.36 to 0.61)**	**0.52 (0.38 to 0.69)**
Nivolumab+ipilimumab vs nivolumab	**0.79 (0.64 to 0.97)**	**0.79 (0.64 to 0.97)**	0.84 (0.68 to 1.04)
Nivolumab+ipilimumab vs pembrolizumab	**0.77 (0.62 to 0.97)**	**0.77 (0.62 to 0.96)**	**0.73 (0.58 to 0.92)**
Nivolumab+ipilimumab vs ipilimumab	**0.36 (0.23 to 0.56)**	**0.36 (0.23 to 0.56)**	0.74 (0.44 to 1.26)
Pembrolizumab vs nivolumab	1.02 (0.76 to 1.35)	1.02 (0.76 to 1.35)	1.16 (0.85 to 1.57)
Nivolumab vs ipilimumab	**0.53 (0.44 to 0.64)**	**0.53 (0.44 to 0.64)**	**0.63 (0.52 to 0.77)**
Pembrolizumab vs ipilimumab	**0.54 (0.44 to 0.67)**	**0.54 (0.44 to 0.67)**	**0.73 (0.58 to 0.92)**

[a] HR<1 favours the first treatment in the comparison over the second treatment. 95% CrIs that do not cross 1 (i.e. statistically significant) for results are highlighted in **bold**
[b] Summary data for BICR-assessed PFS included from the RELATIVITY-047 trial and investigator-assessed PFS for the CheckMate 067, CheckMate 069 and KEYNOTE-006[19] trials
[c] Summary data for investigator-assessed PFS from all trials
BICR=blinded independent central review; CrI=credible intervals; EAG=External Assessment Group; HR=hazard ratio; NMA=network meta-analysis; OS=overall survival; PFS=progression-free survival
Source: EAG analysis using statistical code in EAG report Appendix 3 (Section 8.3) applied to the data in EAG report Appendix 2 (Section 8.2, Table 61)

Table 67 EAG fixed-effect NMA results: ORR and safety outcomes

Comparison	OR (95% CrI)				
	ORR[a]	Grade 3 to 4 AEs[b]	Grade 3 to 4 TRAEs[b]	Discontinuation due to AEs[b]	Discontinuation due to TRAEs[b]
Nivolumab-relatlimab vs nivolumab+ipilimumab	0.84 (0.55 to 1.31)	**0.49 (0.31 to 0.76)**	**0.43 (0.25 to 0.73)**	**0.36 (0.21 to 0.63)**	**0.49 (0.27 to 0.90)**
Nivolumab-relatlimab vs nivolumab	**1.52 (1.13 to 2.08)**	**1.39 (1.03 to 1.88)**	**2.08 (1.39 to 3.13)**	**1.60 (1.09 to 2.34)**	**2.20 (1.40 to 3.53)**
Nivolumab-relatlimab vs pembrolizumab	1.32 (0.70 to 2.51)	NE	**1.99 (1.03 to 3.86)**	1.36 (0.66 to 2.77)	1.73 (0.76 to 3.90)
Nivolumab-relatlimab vs ipilimumab	**5.58 (3.53 to 8.94)**	0.85 (0.55 to 1.32)	**1.72 (1.01 to 2.94)**	1.48 (0.84 to 2.61)	**1.95 (1.03 to 3.71)**
Nivolumab+ipilimumab vs nivolumab	**1.80 (1.32 to 2.46)**	**2.86 (2.08 to 3.97)**	**4.85 (3.46 to 6.82)**	**4.35 (3.00 to 6.42)**	**4.53 (3.10 to 6.75)**
Nivolumab+ipilimumab vs pembrolizumab	1.57 (0.90 to 2.72)	NE	**4.62 (2.83 to 7.54)**	**3.71 (2.12 to 6.55)**	**3.56 (1.90 to 6.55)**
Nivolumab+ipilimumab vs ipilimumab	**6.55 (4.71 to 9.30)**	**1.75 (1.26 to 2.44)**	**3.97 (2.94 to 5.47)**	**4.06 (2.80 to 5.87)**	**3.97 (2.83 to 5.70)**
Pembrolizumab vs nivolumab	1.15 (0.66 to 2.03)	NE	1.05 (0.63 to 1.77)	1.17 (0.64 to 2.16)	1.28 (0.66 to 2.53)
Nivolumab vs ipilimumab	**3.63 (2.56 to 5.21)**	**0.61 (0.44 to 0.84)**	0.83 (0.58 to 1.17)	0.92 (0.61 to 1.42)	0.88 (0.57 to 1.35)
Pembrolizumab vs ipilimumab	**4.22 (2.75 to 6.55)**	NE	0.86 (0.59 to 1.27)	1.08 (0.71 to 1.68)	1.13 (0.68 to 1.92)

[a] OR>1 favours the first treatment in the comparison over the second treatment for ORR. 95% CrIs that do not cross 1 for results highlighted in **bold**

[b] OR<1 favours the first treatment in the comparison over the second treatment for safety outcomes. 95% CrIs that do not cross 1 for results highlighted in **bold**

[c] not estimable for comparisons vs pembrolizumab as Grade 3-4 AEs were not reported for the KEYNOTE-006 trial

AEs=adverse events; CrI=credible intervals; EAG=External Assessment Group; NE=not estimable; NMA=network meta-analysis; OR=odds ratio; ORR=objective response rate; TRAEs=treatment related adverse events

Source: EAG analysis using statistical code in Appendix 3 (Section 8.3 above) applied to the data in Appendix 2 (Section 8.2, Table 62 and Table 63) of this EAG report

8.6 *Appendix 6: EAG investigator-assessed PFS modelling, RELATIVITY-047 trial*

All analyses were carried out in R version 4.2.0.

The EAG fitted standard fully parametric models to the reconstructed investigator-assessed PFS data; the process included assessment of statistical fit and face validity. The investigator-assessed PFS data exhibit a sharp drop at 3 months (Figure 8); this is in line with the protocol-driven timing of the RELATIVITY-047 trial initial tumour assessment. The EAG considered that the standard fully parametric models did not have good face validity since none of the fitted models sufficiently accounted for the protocol-driven shape of the K-M data (baseline to 3 months). Fully parametric model fits, hazards and fit statistics for nivolumab-relatlimab and nivolumab investigator-assessed PFS from the RELATIVITY-047 trial are shown in

Figure 9,

Figure 10,

Figure 11, Figure 12 and Table 68 respectively.

Figure 8 investigator-assessed PFS, nivolumab, RELATIVITY-047 trial

PFS=progression-free survival
Source: CS, Appendix D, Figure 4 and Figure 5 (EAG reproduction)

Figure 9 Investigator-assessed PFS survival curves, fully parametric, nivolumab-relatlimab, RELATIVITY-047 trial

PFS=progression-free survival
Source: EAG modelling

Figure 10 Investigator-assessed PFS hazards, fully parametric, nivolumab-relatlimab, RELATIVITY-047 trial

PFS=progression-free survival
Source: EAG modelling

Figure 11 Investigator-assessed PFS survival, fully parametric, nivolumab, RELATIVITY-047 trial

PFS=progression-free survival

Source: EAG modelling

Figure 12 Investigator-assessed PFS hazards, fully parametric, nivolumab, RELATIVITY-047 trial

PFS=progression-free survival
Source: EAG modelling

Table 68 Fit statistics for the parametric curves fitted to RELATIVITY-047 trial investigator-assessed PFS data

Parametric curve	Nivolumab-relatlimab		Nivolumab	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC=Akaike information criterion, BIC= Bayesian information criterion, PFS=progression-free survival
Source: EAG modelling

The EAG fitted piecewise K-M+parametric models to the reconstructed RELATIVITY-047 trial investigator-assessed PFS data. Assessment of the hazard profile for both nivolumab-relatlimab and nivolumab supported the use of a 3 month cut point for both treatments. The fitted K-M+parametric models, hazards and fit statistics for RELATIVITY-047 trial nivolumab-relatlimab and nivolumab investigator-assessed PFS are shown in Figure 13, Figure 14, Figure 15, Figure 16 and Table 69 respectively.

Figure 13 Investigator-assessed PFS survival, K-M+parametric, nivolumab-relatlimab, RELATIVITY-047 trial

Source: EAG modelling

Figure 14 Investigator-assessed PFS hazards, K-M+parametric, nivolumab-relatlimab, RELATIVITY-047

EAG=External Assessment Group; K-M=Kaplan-Meier; PFS=progression-free survival
Source: EAG modelling

Figure 15 Investigator-assessed PFS survival, K-M+parametric, nivolumab, RELATIVITY-047

EAG=External Assessment Group; K-M=Kaplan-Meier; PFS=progression-free survival
Source: EAG modelling

Figure 16 Investigator-assessed PFS hazards, K-M+parametric, nivolumab, RELATIVITY-047 trial

EAG=External Assessment Group; K-M=Kaplan-Meier; PFS=progression-free survival
Source: EAG modelling

Table 69 EAG fit statistics for the RELATIVITY-047 trial investigator-assessed PFS K-M+parametric curves

Curve	Nivolumab-relatlimab		Nivolumab	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC=Akaike information criterion; BIC= Bayesian information criterion; EAG=External Assessment Group; PFS=progression-free survival
Source: EAG modelling

Since mixture-cure models were not fitted, the EAG instead required that the chosen model should tend towards background mortality hazards at around [redacted] months, to reflect the hazard profiles for both RELATIVITY-047 trial arms (Figure 17) and as expected for nivolumab based on examination of CheckMate 067 trial[5] hazards (Figure 19). Fitted generalised gamma and Gompertz distributions returned the lowest AIC and BIC statistics, but only the Gompertz curve met the criterion that hazards should tend to zero in the short- to medium term.

The EAG compared the relative hazard profiles for the fitted nivolumab+relatlimab K-M+Gompertz models against the hazards from the RELATIVITY-047 trial (Figure 17 and Figure 18). The EAG is satisfied that the relative hazards from the fitted nivolumab-relatlimab curve had face validity versus nivolumab.

The EAG compared the relative hazard profiles for the fitted nivolumab+relatlimab K-M+Gompertz models against the hazards from the RELATIVITY-047 trial (Figure 17 and Figure 18) and the nivolumab investigator-assessed PFS Gompertz curve hazards with external data from the CheckMate-057 trial[5] (Figure 19) to assess plausibility. The nivolumab investigator-assessed PFS estimates align with CheckMate-067 trial[5] nivolumab investigator-assessed PFS data since, in both cases, hazards reach general population levels at around [redacted] (Figure 19 and Figure 16). Further, nivolumab CheckMate-067 trial[5] investigator-assessed PFS is 29% at 5 years (Figure 20), which is similar to the [redacted] predicted by the EAG's K-M+Gompertz curve. The EAG is therefore satisfied that modelling investigator-assessed PFS using a K-M+Gompertz model produces outcomes with face validity for nivolumab.

Figure 17 RELATIVITY-047 trial long-term observed progression/mortality hazards* (investigator-assessed PFS)

* Using B-splines (bshazard package)
PFS=progression-free survival
Source: EAG modelling

[redacted]

Figure 18 Nivolumab-relatlimab and nivolumab investigator-assessed PFS K-M+Gompertz model hazards

K-M=Kaplan-Meier; PFS=progression-free survival
Source: EAG modelling

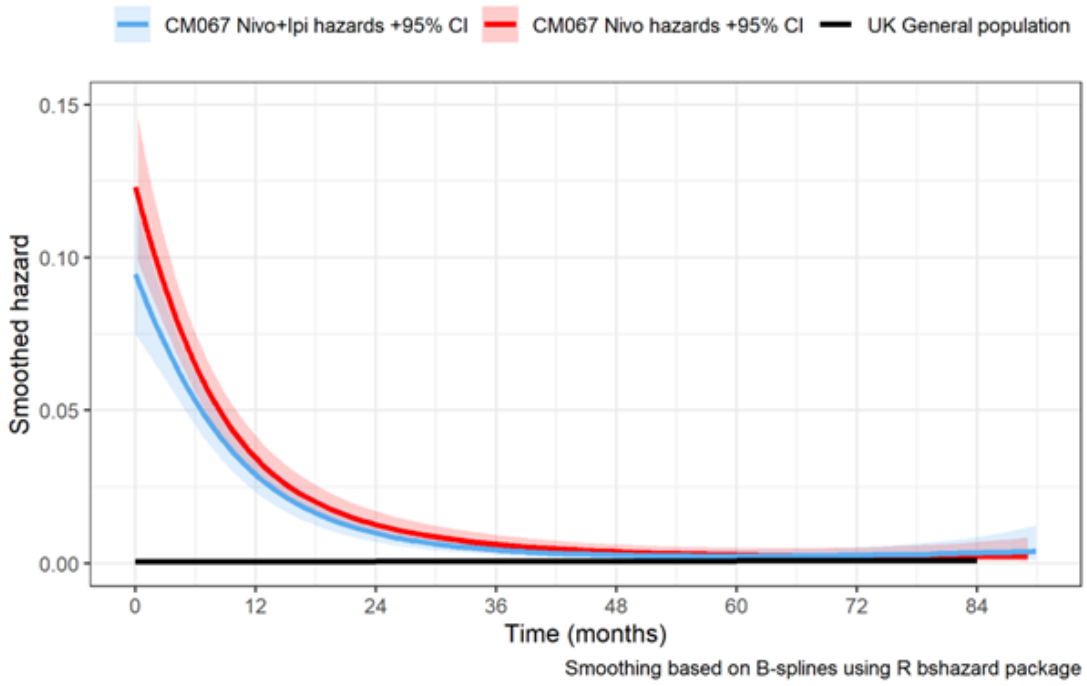

Figure 19 CheckMate-067 trial long-term observed progression/mortality hazards

Source: CS, Figure 21

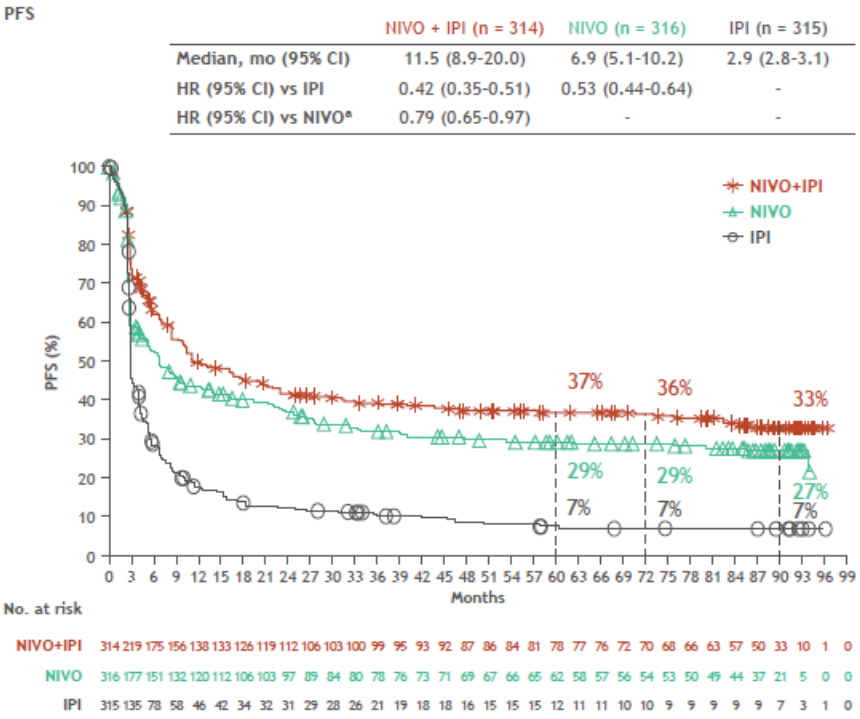

Figure 20 Long-term CheckMate-067 trial PFS data

PFS=progression-free survival
Source: CS, Figure 19

8.7 *Appendix 7: EAG revisions to company model*

EAG revision number and description (see Section 6.10)	Implementation instructions
Severity modifier calculations	**Insert sheet named "EAG Revisions"** In cell C4 enter text "Severity modifier calcs" Set value in cell D4 = 1 In Sheet 'Life Tables' Set value in cell AU14 =IF('EAG Revisions'!D$4=1, ((AM14*INDEX($Z$14:$Z$114,MATCH(AJ14+$AU$10,Y$14:Y$2102,1)))+(AN14*INDEX($AA$14:$AA$114,MATCH(AJ14+$AU$10,Y$14:Y$2102,1)))), ((AM14*INDEX($Z$14:$Z$114,MATCH(AJ14+$AU$10,Y14:Y2102,1)))+(AN14*INDEX($Z$14:$Z$114,MATCH(AJ14+$AU$10,$AA$14:$AA$114,1)))))*$AT14 Copy cell AU14 Paste formulas to range AU14:AU71
FP NMA model parameter sampling corrected – only affects company base case probabilistic results	In Sheet 'OS Data' Highlight rows 92:93 and insert rows Enter text "Nivolumab+ipilimumab" into cells G92 & G93 Enter text "Pembrolizumab" into cell G94 & G95 Enter text "d0" into cell J92 Enter text "d2" into cell J93 Copy range J92:J93 Paste values in cell J94 Set value in cell N92 =i_NMA_OS_NIVO_IPI_d0

EAG revision number and description (see Section 6.10)	Implementation instructions
	Set value in cell N93 =i_NMA_OS_NIVO_IPI_d2 Set value in cell N94 =i_NMA_OS_PEM_d0 Set value in cell N95 =i_NMA_OS_PEM_d2 Set value in cell U92 =F134 Set value in cell V92 =I134*SQRT(F134*H134) Set value in cell U93 = I134*SQRT(F134*H134) Set value in cell V93 =H134 Set value in cell U94 =F135 Set value in cell V94 =I135*SQRT(F135*H135) Set value in cell U95 =I135*SQRT(F135*H135) Set value in cell V95 =H135 Set value in cell T92 IF(Parameters!Y382=4,RAND(),0.5) Copy cell T92 Paste formula in range T92:T93 Set value in cell T94 =IF(Parameters!Y380=4,RAND(),0.5) Copy cell T94 Paste formula in range T94:T95 Set value in cell Q92 =MultiNormInv(T92:T93,N92:N93,U92:V93) Copy cell Q92 Paste formula to cell Q94 In Sheet ‘PFS Data’ Highlight rows 120:123 and insert rows Enter text “Nivolumab+ipilimumab” into cells G121 & G122 Enter text “Pembrolizumab” into cell G123 & G125

EAG revision number and description (see Section 6.10)	Implementation instructions
	Enter text “d0” into cell J121 Enter text “d2” into cell J122 Copy range J121:J122 Paste values in cell J123 Set value in cell N92 =i_NMA_PFS_NIVO_IPI_d0 Set value in cell N93 =i_NMA_PFS_NIVO_IPI_d2 Set value in cell N94 =i_NMA_PFS_PEM_d0 Set value in cell N95 =i_NMA_PFS_PEM_d2 Set value in cell U121 =F166 Set value in cell V121 =I166*SQRT(F166*H166) Set value in cell U122 =I166*SQRT(F166*H166) Set value in cell V122 =H166 Set value in cell U123 =F167 Set value in cell V123 =I167*SQRT(F167*H167) Set value in cell U124 =I167*SQRT(F167*H167) Set value in cell V124 =H167 Set value in cell T121 =IF(Parameters!Y387=4,RAND(),0.5) Copy cell T121 Paste formula in range T121:T122 Set value in cell T123 =IF(Parameters!Y385=4,RAND(),0.5) Copy cell T123 Paste formula in range T123:T124 Set value in cell Q121 =MultiNormInv(T121:T122,N121:N122,U121:V122)

EAG revision number and description (see Section 6.10)	Implementation instructions
	Copy cell Q121 Paste formula to cell Q123 <u>In Sheet 'Parameters'</u> Delete values in range O380:V388 Set value in cell V380 ='OS Data'!Q94 Copy cell V380 Paste formula to range V380:V381 Set value in cell V382 ='OS Data'!Q92 Copy cell V382 Paste formula to range V382:V383 Set value in cell V385 ='PFS Data'!Q123 Copy cell V385 Paste formula to range V385:V386 Set value in cell V387 ='PFS Data'!Q121 Copy cell V387 Paste formula to range V387:V388
R1) RELATIVITY-047 trial PFS (investigator-assessed)	<u>In Sheet 'EAG Revisions'</u> In cell C5 enter text "R1" Set value in cell D5 = 1 <u>In Sheet 'PFS'</u> Unmerge columns HG:HI and columns HJ:HL

EAG revision number and description (see Section 6.10)	Implementation instructions
	Copy range 'PFS IA'!B4:H91 from EAG Revisions Data.xlsx workbook Paste values in cell HD138 Set value in cell AN140 =IF($F140=0,1,INDEX($GS$140:$GS$358,MATCH($F140,$GQ$140:$GQ$358,1)))*IF('EAG Revisions'!D$5=1,0,1)+IF($F140=0,1,INDEX($HF$140:$HF$358,MATCH($F140,$HD$140:$HD$358,1)))*IF('EAG Revisions'!D$5=1,1,0) Copy cell AN140 Paste formula to range AN140:AN807 Set value in cell BI140 =IF($F140=0,1,INDEX($GV$140:$GV$298,MATCH($F140,$GT$140:$GT$298,1)))*IF('EAG Revisions'!D$5=1,0,1)+IF($F140=0,1,INDEX($HJ$140:$HJ$298,MATCH($F140,$HH$140:$HH$298,1)))*IF('EAG Revisions'!D$5=1,1,0) Copy cell BI140 Paste formula to range BI140:BI807 In Sheet 'PFS Data' Copy range N47:N74 Paste values to range AA47:AA74 Copy range J4:J33 from EAG Revisions Data.xlsx workbook Paste values to range Z47:Z74 Set value in cell N47 =IF('EAG Revisions'!$D$5=1,Z47,AA47) Copy cell N47 Paste formula to range N47:N74

EAG revision number and description (see Section 6.10)	Implementation instructions
R2) Pembrolizumab OS/PFS set equal to nivolumab OS/PFS	In Sheet 'Controls' In cell I102 select "Equal to Nivolumab" In cell I133 select "Equal to Nivolumab"
R3) Constant HRs from company's adjusted ITC for nivolumab+ipilimumab	In Sheet 'Controls' In cell I98 select "Constant HR" In cell I129 select "Constant HR" In Sheet 'EAG Revisions' In cell C6 enter text "R3" Set value in cell D6 = 2 Copy range 'Adjusted ITC HRs'!C3:K6 from EAG Revisions Data.xlsx workbook In Sheet 'OS Data' Paste values in cell P132 Set value in cell M134 =IF('EAG Revisions'!$D6=0,P134,IF('EAG Revisions'!$D6= 1, S134,V134)) Copy cell M134 Paste formula to range M134:O134 Set value in cell M135 =IF(OR('EAG Revisions'!$D6=0, 'EAG Revisions'!$D6=2), P135, S135) Copy cell M135 Paste formula to range M135:O135 Copy range 'Adjusted ITC HRs'!C10:K13 from EAG Revisions Data.xlsx workbook

EAG revision number and description (see Section 6.10)	Implementation instructions
	In Sheet 'PFS Data' Paste values in cell S164 Set value in cell P166 =IF('EAG Revisions'!$D6=0,S166,IF('EAG Revisions'!$D6= 1, V166,Y166)) Copy cell P166 Paste formula to range P166:R166 Set value in cell P167 =IF(OR('EAG Revisions'!$D6=0, 'EAG Revisions'!$D6=2), S167,V167) Copy cell P167 Paste formula to range P167:R167 In Sheet 'OS' Set value in cell EG132 =IF($F132=0,1,(DT132^$EG$125))*IF(OR('EAG Revisions'!$D6=0,'EAG Revisions'!$D6=2),1,0)+IF($F132=0,1,(DZ132^$EG$125))*IF('EAG Revisions'!$D6=1,1,0) Copy cell EG132 Paste formula to range EG132: EG798 Set value in cell EN132 =IF($F133=0,1,(DT132^$EN$125))*IF('EAG Revisions'!D$6= 0,1,0)+IF($F133=0,1,(DZ132^$EN$125))*IF('EAG Revisions'!D$6>0,1,0) Copy cell EN132 Paste formula to range EN132:EN798 In Sheet 'PFS' Set value in cell FV140= IF($F140=0,1,(FJ140^FV$133))*IF(OR('EAG Revisions'!D$6=0, 'EAG Revisions'!D$6=2),1,0)+IF($F140=0,1,(FP140^FV$133))*IF('EAG Revisions'!D$6=1,1,0)

EAG revision number and description (see Section 6.10)	Implementation instructions
	Copy cell FV140 Paste formula to range FV140:FV807 Set value in cell GC140= IF($F140=0,1,(FJ140^GC$133))*IF(OR('EAG Revisions'!D$6=0,'EAG Revisions'!D$6=2),1,0)+IF($F140=0,1,(FP140^GC$133))*IF('EAG Revisions'!D$6=1,1,0) Copy cell GC140 Paste formula to range GC140:GC807 In Sheet 'Parameters' Set value in cell G400 to "Yes" Set value in cell G403 to "Yes"
R4) Nivolumab AE cost and disutility values applied to nivolumab+ipilimumab arm after three model cycles (four treatment cycles)	In Sheet 'EAG Revisions' In cell C7 enter text "R4" Set value in cell D7 =1 In Sheet 'NIVO+IPI' Set value in cell AZ18 =AN18*IF(AND('EAG Revisions'!D$7=1,BF17=1),NIVO!AZ$6,AZ$6) Copy cell AZ18 Paste formula to range AZ18:AZ677 Set value in cell BW17 =AN17*IF(AND('EAG Revisions'!D$7=1,BF17=1),NIVO!BW$6,BW$6) Copy cell BW17 Paste formula to range BW17:BW677
R5) TTD constraint (≤ PFS)	In Sheet 'Controls'

EAG revision number and description (see Section 6.10)	Implementation instructions
removed	In cell I147 select “No” In cell I156 select “No” In cell I162 select “No” In cell I168 select “No”
R6a) 2 year stopping rules for IO therapies removed	In Sheet ‘Controls’ In cell H173 select “No” In cell H174 select “No” In cell H175 select “No” In cell H176 select “No”
R6b) 2 year stopping rule removed; plus nivolumab+ipilimumab K-M data used up to [redacted] years and nivolumab TTD hazards applied thereafter	In Sheet ‘EAG Revisions’ In cell C8 enter text “R6b” Set value in cell D8 =1 In Sheet ‘TTD’ Set value in cell AS132 = IF(AND('EAG Revisions'!D$8=1,AE132>'TTD Data'!S$313),AS131*(AA132/AA131), IF(AS$119="Yes",MIN(AN132,PFS!GL140),AN132)) Copy cell AS132 Paste formula to range AS132:AS798
R7) Alternative subsequent treatment cost calculations	In Sheet ‘EAG Revisions’ In cell C9 enter text “R7” Set value in cell D9 =1 In Sheet ‘Subsequent Tx Costs’

EAG revision number and description (see Section 6.10)	Implementation instructions
	Set value in cell E42 =IF('EAG Revisions'!D9=1,sub_comp1_proportion,53%) Set value in cell E43 =IF('EAG Revisions'!D9=1,48%,59%) Set value in cell E44 =IF('EAG Revisions'!D9=1,35%,46%) Set value in cell E45 =IF('EAG Revisions'!D9=1,48%,59%) Set value in cell E52 =IF('EAG Revisions'!D9=1,F52,G52) Set value in cell E53 =IF('EAG Revisions'!D9=1,F53,G53) Set value in cell E64 =IF('EAG Revisions'!D9=1,F64,8.81) In Sheet 'Parameters' Set value in cell AF55 =M55 Set value in cell AF56 =M56 Set value in cell AG55 =SUM(AF55:AF56) Set value in cell AH55 =GAMMA.INV(S55,AF55,1) Set value in cell AH56 =GAMMA.INV(S56,AF56,1) Set value in cell AI55 =SUM(AH55:AH56) Set value in cell AE55 =AH55/AI$55 Set value in cell AE56 =AH56/AI$55 Set value in cell AB55 =IF(Z55="",CHOOSE(Y55,I55,T55,U55,IF('EAG Revisions'!D$9,AE55,V55)),Z55)*IF(L55="",1,L55) Set value in cell AB56 =IF(Z56="",CHOOSE(Y56,I56,T56,U56,IF('EAG Revisions'!D$9,AE56,V56)),Z56)*IF(L56="",1,L56)
R8) EAG change to IV	In Sheet 'EAG Revisions'

EAG revision number and description (see Section 6.10)	Implementation instructions
administration costs	In cell C10 enter text “R8” Set value in cell D10 =1 <u>In Sheet ‘Drug Costs’</u> Set value in cell E65 =IF(‘EAG Revisions’!D10=1,342.66,471) Set value in cell E67 =IF(‘EAG Revisions’!D10=1,281.11,526.52) <u>In Sheet ‘Subsequent Tx Costs’</u> Set value in cell V89 =IF('EAG revisions'!D10=1,Parameters!AB35,INDEX(p_adm_array_costs,MATCH(N89,adm_array_types,0)))*M89 Set value in cell V105 =IF('EAG revisions'!D10=1,Parameters!AB35,INDEX(p_adm_array_costs,MATCH(N105,adm_array_types,0)))*M105 <u>In Sheets ‘NIVO-RELA’, ‘NIVO’ & ‘PEM’</u> Set value in cell BS17 =IF(‘EAG Revisions’!$D$10=1,AN17*((BF17+BH17)*BS$6),AN17*((BF17*BS$7)+(BH17*BS$6))) Copy cell BS17 Paste formula to range BS17:BS677 <u>In Sheet ‘NIVO+IPI’</u> Set value in cell BS6 =IF(‘EAG Revisions’!D10=1,’Drug Costs’!U83/’Drug Costs’!J78*(misc_daysPerMonth/7),INDEX(adm_component1_cost_induction,$D$4)) Set value in cell BS7 =IF(‘EAG Revisions’!D10=1,’Drug Costs’!W76,INDEX(adm_component1_cost,$D$4))

EAG revision number and description (see Section 6.10)	Implementation instructions
EAG exploratory scenarios	

R9) Nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD	In Sheet 'EAG Revisions'
	
	In cell C11 enter text "R9"
	Set value in cell D11 =1
	
	In Sheet 'OS'
	
	Set value in cell EW132 =IF('EAG Revisions'!D$11=1,EU132,EK132)
	
	Copy cell EW132
	
	Paste formula to range EW132:EW799
	
	In Sheet 'PFS'
	
	Set value in cell GL140 =IF('EAG Revisions'!D$11=1,GJ140,FZ140)
	
	Copy cell GL140
	Paste formula to range GL140:GL807
	
	In Sheet 'TTD'
	
	Set value in cell AS132 =IF('EAG Revisions'!D$11=1,AQ132,
	IF(AND('EAG Revisions'!D$8=1,AE132>'TTD Data'!S$313),AS131*(AA132/AA131),
	IF(AS$119="Yes",MIN(AN132,PFS!GL140),AN132)))
	
	Copy cell AS132
	Paste formula to range AS132:AS798

EAG revision number and description (see Section 6.10)	Implementation instructions
R10) General population utility from point of background mortality hazards	In Sheet 'EAG Revisions' In cell C12 enter text "R10" Set value in cell D12 =1 In Sheet 'OS' Set value in cell DS132 =$DP131>DU131 Copy cell DS132 Paste formula to range DS132:DS798 Copy range DS132:DS798 Paste formula to range DY132:DY798 Set value in cell EF132 =$DP132>EI132 Copy cell EF132 Paste formula to range EF132:EF798 Copy range EF132:EF798 Paste formula to range EM132:EM798 In Sheet 'NIVO-RELA' Set value in cell BB6 =INDEX(PFS!F140:F807,MATCH(TRUE,PFS!FI140:FI807,0))+1 Set value in cell BC6 = INDEX(OS!F132:F798,MATCH(TRUE,OS!DS132:DS798,0))+1 Set value in cell AV18 =AQ18*IF(AND('EAG Revisions'!$D$12=1,$M18>=BB$6),INDEX('Life Tables'!$AE$14:$AF$2102,$M18,2),$AU18*AV$6) Copy cell AV18

EAG revision number and description (see Section 6.10)	Implementation instructions
	Paste formula to range AV18:AW677 In Sheet 'NIVO' Set value in cell BB6 =INDEX(PFS!F140:F807,MATCH(TRUE,PFS!FO140:FO807,0))+1 Set value in cell BC6 =INDEX(OS!F132:F798,MATCH(TRUE,OS!DY132:DY798,0))+1 Set value in cell AV18 =AQ18*IF(AND('EAG Revisions'!$D$12=1,$M18>=BB$6),INDEX('Life Tables'!$AE$14:$AF$2102,$M18,2),$AU18*AV$6) Copy cell AV18 Paste formula to range AV18:AW677 In Sheet 'NIVO+IPI' Set value in cell BB6 =INDEX(PFS!F140:F807,MATCH(TRUE,PFS!FU140:FU807,0))+1 Set value in cell BC6 =INDEX(OS!F132:F798,MATCH(TRUE,OS!EF132:EF798,0))+1 Set value in cell AV18 =AQ18*IF(AND('EAG Revisions'!$D$12=1,$M18>=BB$6),INDEX('Life Tables'!$AE$14:$AF$2102,$M18,2),$AU18*AV$6) Copy cell AV18 Paste formula to range AV18:AW677 In Sheet 'PEMBRO' Set value in cell BB6 =INDEX(PFS!F140:F807,MATCH(TRUE,PFS!GB140:GB807,0))+1 Set value in cell BC6 =INDEX(OS!F132:F798,MATCH(TRUE,OS!EM132:EM798,0))+1 Set value in cell AV18 =AQ18*IF(AND('EAG Revisions'!$D$12=1,$M18>=BB$6),INDEX('Life

EAG revision number and description (see Section 6.10)	Implementation instructions
	Tables'!$AE$14:$AF$2102,$M18,2),$AU18*AV$6) Copy cell AV18 Paste formula to range AV18:AW677

Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 10 July 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Evidence in adolescent population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 28: Clinical advice to the EAG is that there is no established NHS treatment pathway for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma; these patients would be managed by oncologists in paediatric cancer centres with input from adult melanoma specialists. The EAG notes that only pembrolizumab is licensed for patients aged ≥12 years[14] but that untreated unresectable or metastatic melanoma is rare in patients aged 12 to 18 years; patients aged <20 years account for only 0.2% of new melanoma cases (all cancer stages) each year in the UK.[2]	NG14 states that "the committee agreed that treatment should not differ between children and adults, and that recommendations also apply to children and young people." Please ensure that the views outlined in NG14 are captured within the text on page 28. "Clinical advice to the EAG is that there is no established NHS treatment pathway for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma; these patients would be managed by oncologists in paediatric cancer centres with input from adult melanoma specialists. <u>As outlined in NG14, the guideline committee agreed that treatment should not differ between children and adults, and that</u>	To ensure all relevant information is considered	Thank you for this comment. Text added as follows (p28): "In NG14, the guideline committee considered that treatment should not differ between children and adults and that recommendations also apply to children and young people."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	recommendations also apply to children and young people. The EAG notes that only pembrolizumab is licensed for patients aged ≥12 years[14] but that untreated unresectable or metastatic melanoma is rare in patients aged 12 to 18 years; patients aged <20 years account for only 0.2% of new melanoma cases (all cancer stages) each year in the UK.[2]"		

Issue 2 Clarification on BICR-assessed PFS versus investigator-assessed PFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: The company considered that the investigator-assessed PFS results were biased in [redacted] but also considered that there was high concordance between BICR-assessed and investigator-assessed PFS in both treatment arms. The EAG considers that RELATIVITY-047 trial BICR-assessed and investigator-assessed PFS data are not concordant.	Remove the text "The EAG considers that RELATIVITY-047 trial BICR-assessed and investigator-assessed PFS data are not concordant." Concordance values are above 80%, there is no rationale for stating that results are not concordant. Replace the word "but" with "and" Use of "but" misleadingly implies that the two concepts (biased PFS results and high concordance) are in contradiction.	To avoid misleading statements	Concordance and bias are not the EAG's main concerns. Text amended to reflect the EAG's main concerns (including deletion of reference to bias and concordance), i.e. "All the company NMAs (estimating constant and time-varying HRs) used BICR-assessed PFS data from the RELATIVITY-047 trial and investigator-assessed PFS from the other three trials. The EAG considers that this approach was not appropriate because BICR-assessed PFS and median investigator-assessed PFS differed in the nivolumab arms ([redacted] months and [redacted] months, respectively). Investigator-assessed PFS was the only PFS outcome available from all four trials included in the PFS NMA. The company also stated (Clarification Question A5) that BICR-assessed PFS and investigator-assessed PFS were

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			separate outcomes of the RELATIVITY-047 trial (i.e., the primary outcome for which the trial was powered, and an exploratory outcome for which the trial was not powered, respectively). Therefore, the company PFS NMAs, which included data from both BICR-assessed PFS and investigator-assessed PFS, are inappropriate and will be impacted by the heterogeneity introduced by the different outcome definitions and assessment methods used. Therefore, only investigator-assessed PFS should have been used for the PFS NMAs."
Page 14: NMA data were not used in the company or the EAG cost effectiveness analyses.	Clarify which NMA data this is referring to (both methodological implementation and approach to estimation; BICR or IA), as results from the time-varying NMA (using the best-available approach to estimation) were used in the company base case cost-effectiveness analysis.	To avoid ambiguous (and potentially misleading) statements	Thank you for highlighting this unclear wording. Text amended as follows (p14): "The effect on the cost effectiveness estimates of using time-varying HRs using investigator-assessed PFS data from all four trials is unknown. Using investigator-assessed PFS data from all four trials, EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			exploratory deterministic analysis results show that treatment with nivolumab-relatlimab dominates nivolumab+ipilimumab and pembrolizumab (PAS prices for nivolumab-relatlimab and nivolumab+ipilimumab, and list prices for pembrolizumab)."
Page 48: "The company considered that investigator-assessed PFS was biased in favour of nivolumab (Clarification Question A5). However, the EAG notes that concordance between the number of BICR-assessed and investigator-assessed PFS events was actually higher in the nivolumab arm ([redacted]) than in the nivolumab-relatlimab arm ([redacted]) at the October 2021 data cut (the company did not provide concordance values for the October 2022 data-cut). The EAG considers that it is not possible for BICR-assessed and investigator-assessed PFS data to be concordant if investigator-	Suggestion to expand the existing text to include the following points, as outlined in Clarification Question A5: • The assessment of nivolumab-relatlimab should utilise PFS per BICR to inform estimates as this is the primary study endpoint in RELATIVITY-047 for which the trial was appropriately powered. PFS per investigator-assessment was an exploratory endpoint for which RELATIVITY-047 was not powered to demonstrate differences by treatment	Current wording lacks sufficient detail for the debate on PFS per BICR versus PFS per investigator-assessment.	Text amended as follows to further signpost the company response to Clarification Question A5 (p48): "The company considered that investigator-assessed PFS was biased [redacted] and that BICR-assessed PFS should be utilised (see Clarification Question A5 for further details)." The EAG has also deleted the following text: "The EAG considers that it is not possible for BICR-assessed and investigator-assessed PFS data to be concordant if investigator-assessed PFS data is biased (as considered by the company)." The EAG notes it can be argued

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
assessed PFS data is biased (as considered by the company)."	• PFS per BICR is referred to as the gold standard for disease progression as it is more objective than PFS per investigator-assessment. This view is well advocated by EMA and FDA guidance[3, 4] • BICR is favoured as it removes assessment bias between readers, reduces variability and increases accuracy in determining if a patient has progressed, thus counteracting many issues that can often arise from investigator-assessment		that these are not necessarily contradictory concepts (as argued by the company above). However, the EAG considers that if one of the outcomes is considered to be biased, and there is high concordance between the outcomes, then it is likely that both outcomes are therefore biased. If, on the other hand, one of the outcomes is considered to be unbiased, and there is high concordance, then it is likely that both outcomes are therefore unbiased. In this instance, as noted by the EAG in the report: "concordance between the number of BICR-assessed and investigator-assessed PFS events was actually higher in the nivolumab arm ([redacted]) than in the nivolumab-relatlimab arm ([redacted]%) at the October 2021 data cut (the company did not provide concordance values for the October 2022 data-cut)." This suggests that contrary to the company's argument, if there is

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			bias, then this may favour nivolumab-relatlimab and not nivolumab. The EAG highlights its concern with the use of BICR-assessed PFS is not in relation to the reporting of results from the RELATIVITY-047 trial but in the use of these data in the PFS NMA (for reasons stated above).
Page 48: "The EAG considers that it is not possible for BICR-assessed and investigator-assessed PFS data to be concordant if investigator-assessed PFS data is biased (as considered by the company)."	Suggestion to remove wording. BICR-assessed and investigator assessed PFS can be concordant, independent of the fact that investigator-assessed PFS is deemed to be more biased than BICR-assessed PFS.	To avoid ambiguous (and potentially misleading) statements	Text deleted for reasons highlighted above.
Page 62/Table 17: "The company did not conduct NMAs to estimate time-varying and constant HRs using RELATIVITY-047 trial investigator-assessed PFS (Clarification Question A9) because of the:	Suggestion to remove the word 'perceived'.	To avoid potentially misleading statement	For clarity, text amended to: "The company did not conduct NMAs to estimate time-varying and constant HRs using RELATIVITY-047 trial investigator-assessed PFS (Clarification Question A9)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• perceived bias in investigator-assessed PFS in favour of the nivolumab arm in the RELATIVITY-047 trial “			because the company: • considered investigator-assessed PFS was biased in favour of the nivolumab arm in the RELATIVITY-047 trial”
Page 22, Table C Page 109 Page 112 Table 52 Page 152 “Constant HRs from adjusted ITC for nivolumab+ipilimumab”	Please clarify that this uses PFS per IA. Please also add a note that where PFS per BICR and PFS per IA give different results, PFS per BICR is less prone to bias.	Provide clarity on the analyses presented and the limitations of these.	Thank you for your suggestions for improving the clarity of the text and these tables. Text/ footnotes added to Table C and Table 52 as follows: “R3) Constant HRs from the company adjusted ITC for nivolumab+ipilimumab” “PFS constant HRs from the company adjusted ITC for investigator-assessed PFS” While PFS per BICR is likely to reduce the risk of bias in trials, as this outcome differs to investigator-assessed PFS, the EAG considers data from the same outcome should be used. Therefore, the company’s suggested note is not relevant and misleading.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			No change made to p152 as the EAG was unable to identify the problem.

Issue 3 Approaches to time to event modelling

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Issue 4 summary table: "Model fit was assessed according to the DIC statistic followed by assessment of the fit of FP curves to K-M data and clinical plausibility of extrapolation estimates. While DIC statistics allow for comparison of the different model fits, they do not provide information about whether a model is a good fit to the data or whether the model estimates are clinically plausible."	Amend text to read: "Model fit was assessed according to the DIC statistic, visual fit of FP curves to K-M data and clinical plausibility of extrapolation estimates. While DIC statistics allow for comparison of the different model fits, they do not provide information about whether a model is a good fit to the data or whether the model estimates are clinically plausible. FP models with clinically implausible survival estimates were not considered for use in the base case analysis."	Current text misleadingly states that DIC statistics were prioritised over the clinical plausibility of curves which was not the case as stated in response to CQ A10. The response highlights that the best fitting models were selected based on both DIC value, visual fit and the clinical plausibility of modelled curves. Notably, the choice of FP model for OS is conservative for nivolumab-relatlimab, as estimates from the best-fitting FP model (which was not used due to issues with clinical plausibility) always gave lower HRs compared to the HRs used in the base case for nivolumab-	Text amended as suggested (p15). The EAG acknowledges that FP models with clinically implausible survival estimates were not considered for use in the base case analysis. However, the company approach to model selection may have disregarded FP models providing clinically plausible results as the visual fit of FP curves to K-M data and clinical plausibility of extrapolation estimates were assessed only for the four FP models with the lowest DIC statistics, some of which provided clinically implausible

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		relatlimab vs all three comparators after 18 months.	curves (EAG report, Table 17). Therefore, the EAG considers that this approach prioritises DIC statistics over clinical plausibility of curves for initial model selection.
Page 15, Issue 4 summary table: "The EAG considers that FP model selection should primarily be based on clinical plausibility of model estimates, including projections of trial data, before model fit statistics are considered."	Amend text to read: "None"	Current text incorrectly implies that model selection was not based on clinical plausibility. This was emphatically not the case, as demonstrated in response to CQ A10.	Please see above response (Issue 4 summary table). No change required.
Page 15, Issue 4 summary table: "Unknown"	Amend text to read: "None"	There is no alternative modelling approach suggested, therefore there will be no impact on cost-effectiveness results.	Please see above response (Issue 4 summary table). No change required.
Page 15, Issue 4 summary table: "Presentation of all PFS and OS FP NMAs that generate clinically plausible results and the corresponding DIC statistics would be informative. Together, this information could be used to	Remove this text.	As per earlier comments, clinically plausible fractional polynomial NMAs were provided in response to CQ A10.	Please see above response (Issue 4 summary table). No change required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ensure that the most appropriate FP model, of all FP models considered, is selected."			
Page 15, Issue 5: "The 95% CrIs around the time-varying HRs reflect the amount of data available overall and not the number of patients providing data at each timepoint. Therefore, the EAG considers that it is not appropriate to infer statistical significance (or lack of) from the FP NMAs 95% CrIs."	This statement requires a supporting reference. Also, this statement requires additional information on how this limitation is resolved via the alternative approaches recommended by the EAG.	Statements made must be evidence-based and balanced.	References are not permitted in the executive summary. However, references to the methods described by Jansen 2011 and Jansen 2012 which support this statement are provided in Table 17 of the EAG report. No change required. This is not a factual inaccuracy. The EAG does not describe an alternative approach. As stated in Issue 5, the EAG is not aware of any existing methods that can be used to adjust FP NMA 95% CrIs to reflect the number of patients providing data at each timepoint. However, the EAG does list the evidence that it considers to be the best available evidence for each comparison.
Page 15, Issue 5 summary table: "Unknown"	Amend text to read: "None"	Difficulties in inferring statistical significance do not affect estimates of cost-effectiveness.	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17, Issue 9 summary table: “nivolumab+ipilimumab: adjusted ITCs”	Expand the existing text to state which ITCs are used in the EAG’s preferred approach.	To improve the clarity of the text.	Text amended as follows: “nivolumab+ipilimumab: company adjusted ITCs (using investigator-assessed PFS data)”
Page 18: “The EAG has run an alternative scenario in which the PFS/OS for pembrolizumab has been set equal to the PFS/OS for nivolumab (RELATIVITY-047 trial data). “Using PAS prices for nivolumab-relatlimab and list prices for pembrolizumab, EAG exploratory deterministic analysis results show that treatment with nivolumab-relatlimab dominates.”	Expand the existing text to also mention the similar scenario analysis included within the company submission	Current text misleadingly implies that this source of uncertainty was not considered in the company submission. The company submission included a scenario in which OS, PFS, and TTD for pembrolizumab were all set equal to nivolumab (Table 84, page 172). This also found that treatment with nivolumab-relatlimab dominates when using PAS prices for nivolumab-relatlimab and list prices for pembrolizumab.	This is not a factual inaccuracy. No change required. Text amended as follows (p18): “In line with company scenario 6, the EAG has run an alternative scenario in which the PFS/OS for pembrolizumab has been set equal to the PFS/OS for nivolumab (RELATIVITY-047 trial data). “Using PAS prices for nivolumab-relatlimab and list prices for pembrolizumab, both the company scenario analysis and EAG alternative scenario results show that treatment with nivolumab-relatlimab dominates.”
Page 75: “The EAG also considers that 95% CrIs around the time-	Remove text: The quoted statement does not rely purely on 95% confidence intervals, but also on the similarity of the HR	Avoid potentially misleading statement	Text amended as follows to remove the quote from the CS (p75):

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
varying HRs cannot be used to infer statistically significant differences between nivolumab-relatlimab and pembrolizumab or to suggest "nivolumab+ipilimumab may perform similarly to nivolumab-relatlimab in terms of OS and PFS" (CS, B.2.9.1.4).	point-estimates to 1 (e.g. for OS from months 12 to 48 it is between 0.98 and 1.02)		"The EAG also considers that 95% CrIs around the time-varying HRs cannot be used to infer statistically significant differences, nor lack of statistically significant difference, nor similarity between nivolumab-relatlimab and pembrolizumab, nor similarity between nivolumab-relatlimab and nivolumab+ipilimumab."
Page 81. "In the absence of direct head-to-head evidence, the company's FP NMA results were applied to nivolumab PFS and OS estimates to generate nivolumab+ipilimumab and pembrolizumab PFS and OS estimates."	Amend text: "In the absence of direct head-to-head evidence and evidence of a lack of proportional hazards within the network of evidence, the company's FP NMA results were applied to nivolumab PFS and OS estimates to generate nivolumab+ipilimumab and pembrolizumab PFS and OS estimates."	Mentioning both justifications for using FP NMAs.	Text amended as follows: "In the absence of direct head-to-head evidence and evidence of a lack of PHs within the network of evidence, the company's FP NMA results were applied to nivolumab PFS and OS estimates to generate nivolumab+ipilimumab and pembrolizumab PFS and OS estimates."
Page 117. "There is no robust evidence for the comparison of nivolumab-relatlimab versus pembrolizumab; the EAG has set	Amend text: "The EAG considers that there is no robust evidence for the comparison of nivolumab-relatlimab versus	Remove subjective language.	Text amended as follows: "The EAG considers that there is no robust evidence for the comparison of nivolumab-

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
pembrolizumab PFS/OS equal to nivolumab PFS/OS (RELATIVITY-047 trial)."	pembrolizumab; the EAG has set pembrolizumab PFS/OS equal to nivolumab PFS/OS (RELATIVITY-047 trial)."		relatlimab versus pembrolizumab…" Text has also been amended earlier in the paragraph where the EAG describes the robustness of the evidence from the RELATIVITY-047 trial as follows: "The EAG considers that the RELATIVITY-047 trial provides robust clinical effectiveness evidence…"

Issue 4 Use of background mortality hazards and general population utility

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 96. The EAG considers that, in the company base case, the magnitude of the differences, between treatments, in the proportion of patients 'cured' in the PD health state (Table 42) is implausible as subsequent treatments are expected to be	Please amend text to read: "Table 42 shows the proportion of patients in the progression-free health state at the point when PFS hazard meet background mortality hazards and the proportion of patients alive when OS hazards meet background mortality hazards	The 'After progression' proportion generated in the current approach is not valid as it uses proportions generated at separate time-points (when PFS hazards equal background mortality hazards and when OS hazards meet background mortality hazards).	This is not a factual inaccuracy. Patients enter the progressed disease health state at different times following progression, therefore it is not accurate to use the model time points to try to assess the proportion of patients cured after progression.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
similar for all patients, regardless of initial treatment.	(note this occur at different time-points). In the company submission it was acknowledged that long-term estimates of PFS were too low for nivolumab-relatlimab, hence estimates of 'after progression' proportion would be inflated. Specifically, in Section B3.3.4.1.2: "extrapolations for nivolumab-relatlimab are likely to underestimate the true long-term PFS of nivolumab-relatlimab, and hence also underestimate its true cost-effectiveness."		The EAG notes (EAG report, p96) that the proportion of patients alive and progression-free or alive at the timepoint when background mortality hazards are used in the model are a proxy for a 'cure' proportion. Text has been added (EAG report, p96) to clarify the use of these proportions as proxies for cure proportions as follows: "can be considered the 'cure' proportion from a non-mixture cure model or an appropriate proxy for a 'cure' proportion from a mixture cure approach. In a mixture cure approach, few 'cured' patients would be expected to have died by the point at which PFS or OS hazards meet background mortality hazards; therefore the 'cure' proportion will not differ substantially from the proportions event free at these times. In the absence of explicit 'cure'

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			proportions from the company modelling, "
Page 96: Table 42	Please remove the 'After Progression' percentages and add time-points for the 'Before Progression' and 'All Patients' percentages. If 'After progression' percentages are included it is essential that this is derived from OS and PFS estimates from the **same** time-point. For example, using OS values at the time that PFS reaches background hazards, the proportions 'after progression' are: nivolumab-relatlimab: 18.3%, nivolumab-ipilimumab: 10.7%, nivolumab: 15.4%. These proportions are similar to that reported for CheckMate 067 (Wolchock 2021 78 month estimates) which provides 'after progression' values ranging from 13% to 15%.	The current approach takes the 'before progression' percentage from the time at which PFS hazards meet background mortality and the 'all patients' percentage from the time at which OS hazards meet background mortality. These occur at two separate time-points and should not be combined to generate an 'After progression' percentage.	This is not a factual inaccuracy. Please see above response (p96). Footnote to Table 42, Table 43 and Table 44 amended to improve clarity: "Proxy 'cure' proportion defined as the time from which background mortality hazards are used in the model."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 99. "Compared to the company BICR-assessed PFS estimates, the EAG investigator-assessed PFS estimates lead to smaller absolute differences, between all treatments, in the proportions of patients expected to be 'cured' in the PD health state (Table 43)." Table 43.	Please remove mention of 'After progression' proportions from the text and note that 'Before progression' and 'All patients' proportions are generated at separate time points. To Table 43 please remove 'After progression' columns and add the time-points at which each percentage is generated.	The current approach takes the 'before progression' percentage from the time at which PFS hazards meet background mortality and the 'all patients' percentage from the time at which OS hazards meet background mortality. These occur at two separate time-points and should not be combined to generate an 'After progression' percentage.	This is not a factual inaccuracy. Please see above response (p96). Footnote to Table 43 amended to improve clarity: "Proxy 'cure' proportion defined as the time from which background mortality hazards are used in the model."

Issue 5 Subsequent treatments

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 87: "In the NICE Melanoma HEMR report[67] distributions are based on clinical advice about NHS clinical practice. Clinical advice was that: • patients with BRAF-mutant tumours receive targeted treatment irrespective of first-line treatment (dabrafenib+trametinib: 50%; encorafenib+binimetinib: 50%). • patients with BRAF-wild type tumours receive ipilimumab in the second-line setting if previously treated with an immunotherapy.	Amend text to read: "In the NICE Melanoma HEMR report[67] distributions are based on clinical advice about NHS clinical practice. Clinical advice was that: • patients with BRAF-mutant tumours receive targeted treatment irrespective of first-line treatment (dabrafenib+trametinib: 50%; encorafenib+binimetinib: 50%). • patients with BRAF-wild type tumours receive ipilimumab in the second-line setting if previously treated with IO monotherapy or would be enrolled in clinical trials if previously treated with combination IO therapy."	To accurately reflect the NICE Melanoma HEMR report, which was used as the main approach for modelling subsequent treatments.	Text amended as follows (p87): "patients with BRAF-wild type tumours receive ipilimumab in the second-line setting if previously treated with IO monotherapy or would be enrolled in clinical trials if previously treated with combination IO therapy."
Page 103: "The subsequent systemic treatment costs presented in CS, Table 65 (weighted by the proportions of patients initiating subsequent treatment) represent a large proportion of total costs,	Amend text to read: "The per patient cost of subsequent treatments presented in CS Table 65 represent a large proportion of total costs when weighted by the proportion of patients initiating subsequent	To improve clarity of the document.	Text amended as follows (p103): "The per patient cost of subsequent treatments presented in CS, Table 65 represent a large proportion of total costs when weighted by the proportion of patients initiating

particularly for the single agent IO therapies (nivolumab-relatlimab: [redacted]%, nivolumab: [redacted]%, nivolumab+ipilimumab: [redacted]%, pembrolizumab: [redacted]%)."	treatment, particularly for IO therapies (nivolumab-relatlimab: [redacted]%, nivolumab: [redacted]%, nivolumab+ipilimumab: [redacted]%, pembrolizumab: [redacted]%)."		subsequent treatment, particularly for the IO monotherapies (nivolumab-relatlimab: [redacted]%, nivolumab: [redacted]%, nivolumab+ipilimumab: [redacted]%, pembrolizumab: [redacted]%)."
Page 104: "Instead, the company used CheckMate 067 trial (5-year OS follow-up)[5] data to estimate the proportions of patients who received any subsequent treatments, including radiotherapy, surgery and investigational procedures."	Amend to read: "Instead, the company followed the committee preferred approach of the NICE Melanoma HEMR, which used CheckMate 067 trial (5-year OS follow-up)[5] data to estimate the proportions of patients who received any subsequent treatments, including radiotherapy, surgery and investigational procedures."	Provide appropriate context (precedence) regarding the approach.	Text amended as follows (p104): "Instead, in line with the NICE Melanoma HEMR committee preferred approach, the company used CheckMate 067 trial (5-year OS follow-up) data to estimate the proportions of patients who received any subsequent treatments, including radiotherapy, surgery and investigational procedures."
Page 104: "In the RELATIVITY-047 trial, the proportions of patients in both trial arms who received subsequent systemic treatments were similar."	Amend text to read: "In the RELATIVITY-047 trial, the proportions of patients in both trial arms who received subsequent systemic treatments were similar, albeit lower in the nivolumab-relatlimab arm ([redacted] for nivolumab-relatlimab, [redacted] for nivolumab). Compared to the nivolumab-relatlimab arm, there was a relative 52% increase in the use of ipilimumab as a	To provide context on subsequent therapies in RELATIVITY-047.	This is not a factual inaccuracy. Text amended as follows (p104): ""In the RELATIVITY-047 trial, the proportions of patients in both trial arms who received subsequent systemic treatments were similar (nivolumab-relatlimab: [redacted], nivolumab: [redacted])."

	subsequent treatment in the nivolumab arm ([redacted] for nivolumab-relatlimab, [redacted] for nivolumab)"		
Page 104: The company has assumed that the proportion of patients receiving subsequent treatment following pembrolizumab was the same as the proportion of patients receiving subsequent treatment following nivolumab (CheckMate 067 trial[5] subsequent systemic treatment data).	Amend text to read: "The company followed the committee preferred approach of the NICE Melanoma HEMR, and assumed that the proportion of patients receiving subsequent treatment following pembrolizumab was the same as the proportion of patients receiving subsequent treatment following nivolumab (CheckMate 067 trial[5] subsequent systemic treatment data)."	Provide appropriate context (precedence) regarding the approach.	Text amended as follow (p104): "The company, in line with the NICE Melanoma HEMR committee preferred approach, assumed that the proportion of patients receiving subsequent treatment following pembrolizumab was the same as the proportion of patients receiving subsequent treatment following nivolumab (CheckMate 067 trial[5] subsequent systemic treatment data)."

Issue 6 Incorrect data points/typing errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: "In the RELATIVITY-047 trial, median investigator-assessed PFS and median BICR-assessed PFS were very similar in the nivolumab-relatlimab arm ([redacted] months and [redacted] months,	Please update text to read: "In the RELATIVITY-047 trial, median BICR-assessed PFS and median investigator-assessed PFS were very similar	Correct reporting of outcomes	Thank you for highlighting this error. The text has been amended to: "In the RELATIVITY-047 trial, median BICR PFS and median investigator-assessed PFS were very similar in the nivolumab-

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
respectively) but differed in the nivolumab arm ([redacted] months and [redacted] months, respectively).” The stated BICR values are those for investigator-assessment, and vice-versa	in the nivolumab-relatlimab arm ([redacted] months and [redacted] months, respectively) but differed in the nivolumab arm ([redacted] months and [redacted] months, respectively).”		relatlimab arm ([redacted] months and [redacted] months, respectively) but differed in the nivolumab arm ([redacted] months and [redacted] months, respectively).”
Page 21: R11) EAG combined exploratory analysis	Present results for R1, R5, R6a, R7, R8, R10	Consistency in reporting results compared with nivolumab+ipilimumab	No change required. The EAG combined exploratory analysis (R11) relates only to the comparison against nivolumab+ipilimumab and is therefore not relevant for other comparators.
Page 22: R9) Incremental QALYs: [redacted] R11) Incremental costs: [redacted] R11) ICER: [redacted]	Please update text to read: R9) Incremental QALYs: [redacted] R11) Incremental costs: [redacted] R11) ICER: [redacted]	Typographical errors	Thank you for highlighting this error. The typographical error for R9 has been corrected. The EAG has not been able to validate the company suggested incremental costs and ICER for R11 and has, therefore, not changed these numbers.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22: R11) EAG combined exploratory analysis (R1, R4-R6a, R7-R9)	R11) EAG combined exploratory analysis (R1, R4-R6b, R7-R9, R10)	Typographical error, and the combined exploratory analyses should not selectively include only some exploratory analyses	There is not a typographical error; R9 (nivolumab-ipilimumab OS/PFS/TTD set equal to nivolumab-relatlimab OS/PFS/TTD) is implemented in place of R6b (nivolumab+ipilimumab K-M data used up to 5.5 years and nivolumab TTD hazards applied thereafter). The EAG combined exploratory analysis (R11) relates only to the comparison against nivolumab+ipilimumab and is therefore not relevant for other comparators.
Page 23: R11) EAG combined exploratory analysis	Present results for R1-R2, R5, R6a, R7-R8, R10	Consistency in reporting results compared with nivolumab+ipilimumab	The EAG combined exploratory analysis (R11) relates only to the comparison against nivolumab+ipilimumab and is therefore not relevant for other comparators.
Page 33: “Nivolumab-relatlimab, nivolumab and ipilimumab are available to the NHS at confidential,	Amend text to read: “Nivolumab-relatlimab, nivolumab, pembrolizumab and ipilimumab are available to the	Acknowledge that all comparators are available to the NHS at PAS prices.	Text amended as follows (p33): “Nivolumab-relatlimab, nivolumab, pembrolizumab and ipilimumab are available to the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
discounted Patient Access Scheme (PAS) prices."	NHS at confidential, discounted Patient Access Scheme (PAS) prices."		NHS at confidential, discounted Patient Access Scheme (PAS) prices."
Page 50-51: "The exceptions were patients recruited in phase III of the RELATIVITY-047 trial, patients recruited in Latin America, patients with baseline metastasis stage M1, patients with cutaneous acral or mucosal histology, patients with ECOG PS of 1 at baseline and patients with both LAG-3 expression ≥1% and PD-L1 tumour expression ≥1%." Patients with both LAG-3 expression ≥ 1% and PD-L1 tumour expression ≥ 1 should be omitted from this list. "Patients with baseline metastasis stage M1" should also be updated to state "Patients with baseline metastasis stage M1a".	Please update text to read: "The exceptions were patients recruited in phase III of the RELATIVITY-047 trial, patients recruited in Latin America, patients with baseline metastasis stage M1a, patients with cutaneous acral or mucosal histology and patients with ECOG PS of 1 at baseline." Please also note, AIC marking is not required here as this information is publicly available in the EPAR	Correct reporting of outcomes	Thank you for highlighting this error. AIC marking removed and text amended as follows: "The exceptions were patients recruited in phase III of the RELATIVITY-047 trial, patients recruited in Latin America, patients with baseline metastasis stage M1a, patients with cutaneous acral or mucosal histology, patients with ECOG PS of 1 at baseline and patients with PD-L1 tumour expression ≥10%."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 54: The HRQoL results for patients off-treatment (Clarification Question A8) showed that: • Time off-treatment questionnaire completion rates were much lower [redacted] Incorrect range reported ([redacted] to [redacted] should be corrected to state to [redacted])	Please update text to read: The HRQoL results for patients off-treatment (Clarification Question A8) showed that: • Time off-treatment questionnaire completion rates were much lower [redacted]	Correct reporting of outcomes	Thank you for highlighting this error. The text has been amended as suggested.
Page 86: This approach is in line with the preferred approach of the NICE Melanoma HEMR[67] Committee preferred approach.	"This approach is in line with the preferred approach of the NICE Melanoma HEMR[67] Committee."	Duplication removed.	Thank you for highlighting this error. The text has been amended as suggested.
Page 91 Figure 3: "Figure 3 Scenario analysis tornado diagram: nivolumab-relatlimab versus	Amend text to read: "Figure 3 Tornado diagram showing the impact on ICER versus nivolumab + ipilimumab	It is unclear from the caption that the figure shows difference from base-case ICERs rather than costs.	Text amended as follows (p91): "Figure 3 Scenario analysis tornado diagram: impact on ICER for nivolumab-relatlimab versus

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
nivolumab+ipilimumab (PAS prices for company assets)"	(PAS prices for company assets)"		nivolumab+ipilimumab (PAS prices for company assets)"
Page 151: "Set value in cell N47 =IF('EAG Revisions'!$D$5=1,Z47,AA47) Copy cell N47 Paste formula to range N47:N74"	This description does not match the formula used in the range N47:N74. Please amend description or model accordingly.	Ensure consistency between report and model	Thank you for highlighting this inconsistency. The formula in the model has been updated accordingly.

Issue 7 Suitability for combination IO therapies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13: "In NG14, it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • for whom IO combination therapy is suitable,	Amend text to read: "In NG14, it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • receive nivolumab+ipilimumab if it is suitable and acceptable	As per NG14, it is important to note that treatment choice is based on both suitability and acceptability. It is also important to be clear that nivolumab + ipilimumab was the only available IO combination treatment at the time of NG14	Text amended as follows to improve clarity: "In NG14, it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • for whom IO combination therapy (currently only nivolumab+ipilimumab) is

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
receive nivolumab+ipilimumab • for whom nivolumab+ipilimumab is **not** suitable receive, pembrolizumab or nivolumab."	• for whom nivolumab+ipilimumab is not suitable or acceptable receive, pembrolizumab or nivolumab."		suitable and acceptable, receive nivolumab+ipilimumab • for whom nivolumab+ipilimumab is **not** suitable or acceptable receive, pembrolizumab or nivolumab."
Page 13: "It is unclear whether the available trial evidence should be used to inform decision-making for the population for whom nivolumab+ipilimumab is not suitable as the RELATIVITY-047 trial, CheckMate 067 trial and CheckMate 069 trial only recruited patients for whom IO combination therapy was considered suitable."	Remove text	The EAG are conflating nivolumab-relatlimab and nivolumab + ipilimumab. These are two different combination treatments and cannot be used interchangeably. The CheckMate 067 and CheckMate 069 trials enrolled patients eligible for nivolumab + ipilimumab as this was an intervention. The RELATIVITY-047 trial enrolled patients who are eligible for nivolumab-relatlimab as this is an intervention. This does not follow that RELATIVITY-047 enrolled patients who were suitable for nivolumab + ipilimumab.	The issue heading and summary text have been amended to improve clarity: "Issue 2 Lack of clinical effectiveness data for NHS patients who currently receive IO monotherapy" "It is unclear whether the available trial evidence should be used to inform decision-making for the population for whom IO combination therapy is not suitable or acceptable as the RELATIVITY-047 trial, CheckMate 067 trial and CheckMate 069 trial only recruited patients for whom IO combination therapy (nivolumab-relatlimab or

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			nivolumab+ipilimumab) was considered suitable and acceptable.”
Page 16: Clinical advice to the EAG is that between 30% and 50% of NHS patients with untreated unresectable or metastatic melanoma are treated with pembrolizumab (or nivolumab); for these patients, an IO combination therapy is not suitable. The EAG considers that the company and EAG cost effectiveness results only relate to patients who are suitable for an IO combination therapy.	Amend text to read: Clinical advice to the EAG is that between 30% and 50% of NHS patients with untreated unresectable or metastatic melanoma are treated with pembrolizumab (or nivolumab); for these patients, nivolumab + ipilimumab is not suitable or not acceptable.”	The only combination IO therapy currently available in the NHS for treatment of advanced melanoma is nivolumab+ipilimumab therefore clinical advice to the EAG will apply specifically to nivolumab + ipilimumab rather than combination IO-therapies broadly. In addition, as per the previous comment, suitability for treatment with nivolumab + ipilimumab was not part of the eligibility criteria for RELATIVITY-047.	Issue heading and summary text amended as follows to improve clarity: “Issue 7 Limited generalisability of company cost effectiveness results to NHS patients for whom IO combination therapy is not suitable or acceptable” “Clinical advice to the EAG is that between 30% and 50% of NHS patients with untreated unresectable or metastatic melanoma are treated with pembrolizumab (or nivolumab); for these patients, an IO combination therapy (currently only nivolumab+ipilimumab) is not suitable or acceptable. The EAG considers that the company and EAG cost effectiveness results only relate to patients for whom IO combination therapy is suitable and acceptable

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			(nivolumab-relatlimab and nivolumab+ipilimumab)."
Page 26-27: In NG14,[9] the evidence showed that IO therapies were more clinically effective and cost effective than targeted therapies (i.e., BRAF inhibitors and mitogen-activated extracellular signal-regulated kinase [MEK] inhibitors) and that IO combination therapies were…	Amend text to read: "In NG14,9 the evidence showed that IO therapies were more clinically effective and cost effective than targeted therapies (i.e., BRAF inhibitors and mitogen-activated extracellular signal-regulated kinase [MEK] inhibitors) and that nivolumab+ipilimumab was…"	The only combination IO therapy currently available in the NHS for treatment of advanced melanoma is nivolumab+ipilimumab therefore clinical advice to the EAG will apply specifically to nivolumab + ipilimumab rather than combination IO-therapies broadly.	Thank you improving the clarity of this text. Text amended as follows: "In NG14,[9] the evidence showed that IO therapies were more clinically effective and cost effective than targeted therapies (i.e., BRAF inhibitors and mitogen-activated extracellular signal-regulated kinase [MEK] inhibitors) and that IO combination therapy (i.e., nivolumab+ipilimumab) was more clinically effective and cost effective than IO monotherapies."
Page 27: "…that IO combination therapies were more clinically effective and cost effective than IO monotherapies. However, it was also noted that the toxicity risk associated with IO therapies was greater than the toxicity risk associated with targeted therapies and that the toxicity risk	Amend text to read: "…that IO combination therapy (nivolumab+ipilimumab) was more clinically effective and cost effective than IO monotherapies. However, it was also noted that the toxicity risk associated with IO therapies was greater than the toxicity risk associated with targeted therapies and that the	To improve accuracy and clarity of the document	Thank you improving the clarity of this text. The text has been amended as follows: "…that IO combination therapy (nivolumab+ipilimumab) was more clinically effective and cost effective than IO monotherapies. However, it was also noted that the toxicity risk associated with IO therapies was greater than the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
associated with IO combination therapies (nivolumab+ipilimumab) was greater than the toxicity risk associated with IO monotherapies (nivolumab and pembrolizumab)."	toxicity risk associated with nivolumab+ipilimumab was greater than the toxicity risk associated with IO monotherapies (nivolumab and pembrolizumab)."		toxicity risk associated with targeted therapies and that the toxicity risk associated with IO combination therapy (nivolumab+ipilimumab) was greater than the toxicity risk associated with IO monotherapies (nivolumab and pembrolizumab).""
Page 27: In NG14,[9] treatment with nivolumab+ipilimumab is the preferred first-line treatment for adult patients with previously untreated unresectable or metastatic melanoma if they are suitable based on the above listed factors. If treatment with nivolumab+ipilimumab is unsuitable for patients, then, in the first-line setting, patients should be treated with pembrolizumab or nivolumab monotherapy.	Amend text to quote directly from NG14: "The NG14 states: 1.8.8 Offer nivolumab plus ipilimumab to people with untreated stage IV or unresectable stage III melanoma if suitable for them based on the factors in recommendation 1.8.6. [2022] 1.8.9 If nivolumab plus ipilimumab is unsuitable or unacceptable (for example, because of potential toxicity),	Nivolumab+ipilimumab is unsuitable for some patients due to adverse events, therefore it is necessary to reflect this in the text	The text has been amended as follows to improve clarity: "In NG14,[9] treatment with nivolumab+ipilimumab is the preferred first-line treatment for adult patients with previously untreated unresectable or metastatic melanoma if suitable and acceptable for patients based on the above listed factors. If treatment with nivolumab+ipilimumab is unsuitable or is not acceptable (e.g., due to potential toxicity) for patients, then, in the first-line setting, patients should be treated with pembrolizumab or nivolumab monotherapy."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	offer pembrolizumab or nivolumab monotherapy. [2022]"		
Page 29, Table 3: "The RELATIVITY-047 trial,[16] CheckMate 067 trial[17] and CheckMate 069 trial[18] only recruited patients for whom IO combination therapy was considered suitable. It is unclear whether the available trial evidence should be used to inform decision-making for patients for whom IO combination therapy is not suitable."	Remove text	As per earlier comments, IO combination treatments cannot be viewed interchangeably; suitability for treatment with nivolumab + ipilimumab was not part of the eligibility criteria for RELATIVITY-047.	The text has been amended as follows to improve clarity: "The RELATIVITY-047 trial,[16] CheckMate 067 trial[17] and CheckMate 069 trial[18] only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable."
Page 31: "In NG14,[9] it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • for whom IO combination therapy is suitable, receive nivolumab+ipilimumab • for whom nivolumab+ipilimumab is	Amend text to read: "In NG14,[9] it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • receive nivolumab+ipilimumab if it is suitable and acceptable • for whom nivolumab+ipilimumab is not suitable or not	As per previous comments, to more accurately reflect both NG14 and RELATIVITY-047	Text amended as follows to improve clarity: "In NG14, it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • for whom IO combination therapy (currently only nivolumab+ipilimumab) is suitable and acceptable,

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
not suitable receive, pembrolizumab or nivolumab. It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial[17] and CheckMate 069 trial[18]) should be used to inform decision-making for the population for whom nivolumab+ipilimumab is not suitable as the these trials only recruited patients for whom IO combination therapy was considered suitable.”	acceptable, receive pembrolizumab or nivolumab.”		receive nivolumab+ipilimumab • for whom nivolumab+ipilimumab is **not** suitable or acceptable receive, pembrolizumab or nivolumab. It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial[17] and CheckMate 069 trial[18]) should be used to inform decision-making for the population for whom nivolumab+ipilimumab is not suitable or acceptable (i.e., NHS patients receiving pembrolizumab or nivolumab monotherapy) as these trials only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable. Clinical advice to the EAG is that the RELATIVITY-047 trial population is representative of

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			adult patients with previously untreated metastatic or unresectable melanoma who are likely to be treated in NHS clinical practice and for whom an IO combination therapy is suitable and acceptable."
Page 33: "if IO combination or monotherapies are unsuitable."	Amend text to read: "If nivolumab+ipilimumab or monotherapies are unsuitable"	The only combination IO therapy currently available in the NHS for treatment of advanced melanoma is nivolumab+ipilimumab therefore clinical advice to the EAG will apply specifically to nivolumab + ipilimumab rather than combination IO-therapies broadly.	Text amended as follows to improve clarity: "if IO combination therapy (currently only nivolumab+ipilimumab) or IO monotherapies are unsuitable or not acceptable."
Page 73: In NG14,[9] it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • for whom IO combination therapy is suitable,	Amend text to read: "In NG14,[9] it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • receive nivolumab+ipilimumab if it is suitable and acceptable	As per previous comments, to more accurately reflect both NG14 and RELATIVITY-047	Text amended (p74) as follows to improve clarity: "In NG14,[9] it is recommended that NHS patients with untreated unresectable or metastatic melanoma: • for whom IO combination therapy (currently only nivolumab+ipilimumab) is suitable and acceptable,

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
receive nivolumab+ipilimumab • for whom nivolumab+ipilimumab is not suitable receive, pembrolizumab or nivolumab. It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial[17] and CheckMate 069 trial[18]) should be used to inform decision-making for the population for whom nivolumab+ipilimumab is not suitable as the these trials only recruited patients for whom IO combination therapy was considered suitable.	• for whom nivolumab+ipilimumab is not suitable or not acceptable, receive pembrolizumab or nivolumab." 		receive nivolumab+ipilimumab • for whom nivolumab+ipilimumab is not suitable or acceptable, receive pembrolizumab or nivolumab. It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial[17] and CheckMate 069 trial[18]) should be used to inform decision-making for the population for whom nivolumab+ipilimumab is not suitable or acceptable (i.e., NHS patients receiving pembrolizumab or nivolumab monotherapy) as these trials only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93: As noted in Section 2.3.2, Section 3.7.1 and Section 3.8, the EAG considers that the company and EAG cost effectiveness results only relate to patients who are suitable for an IO combination therapy”	Remove text	As per earlier comments, IO combination treatments cannot be viewed interchangeably; suitability for treatment with nivolumab + ipilimumab was not part of the eligibility criteria for RELATIVITY-047.	This is not a factual inaccuracy. Text amended (p94) as follows to improve clarity: As noted in Section **Error! Reference source not found.**, Section **Error! Reference source not found.** and Section **Error! Reference source not found.**, the EAG considers that the company and EAG cost effectiveness results only relate to patients for whom an IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) is considered suitable and acceptable.
Page 93: “However, the EAG considers that the company and EAG cost effectiveness results only relate to patients who are suitable for an IO combination therapy.”	Remove text	As per earlier comments, IO combination treatments cannot be viewed interchangeably; suitability for treatment with nivolumab + ipilimumab was not part of the eligibility criteria for RELATIVITY-047.	This is not a factual inaccuracy. Text amended as follows to improve clarity: “However, the EAG considers that the company and EAG cost effectiveness results only relate to patients for whom an IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) is

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			considered suitable and acceptable.”

Issue 8 Treatment duration

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18. “In addition, no stopping rules were specified in the NICE recommendations for nivolumab, pembrolizumab or nivolumab+ipilimumab as treatments for advanced melanoma.”	Either remove text, or add notes for the following: • That 2-year stopping rules were included in the base case analyses that informed decision-making for all three appraisals and a two-year stopping rule was included in the NICE Melanoma HEMR. • That it is unusual for stopping rules to be specified in the NICE recommendations. For example the following nivolumab appraisals had stopping rules in trials but not recommendations: TA817, TA818, TA857, TA865. Similarly TA366	To provide appropriate context.	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	(Pembrolizumab for advanced melanoma not previously treated with ipilimumab) did not include a stopping rule in its recommendation. (this is just a small set of examples, not intended to be exhaustive). • Add examples of where stopping rules are specified in the NICE recommendations		
Page 18. "The company has assumed that all treatment with all IO therapies stops at 2 years."	Amend text: "The company modelled a two-year stopping rule for IO therapies. This was based on clinical advice, previous NICE appraisals, and the NICE Melanoma HEMR which noted "In clinical practice, the committee felt strongly that patients would not continue treatment beyond two years, based on their clinical experience…as clinician experience and confidence in treatment with these therapies	To provide appropriate context.	Text amended as follows (p18): "The company has assumed that all treatment with all IO therapies stops at 2 years (based on clinical advice and NICE melanoma HEMR)."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	has grown, they are happy to stop treatment at two years and can be sure of an ongoing immune response". It is also consistent with clinical advice received by the EAG."		
Page 18. What additional evidence or analyses might help to resolve this key issue? "None"	Amend "None" to: "Evidence from clinical trials, real-world studies, and clinical opinion regarding likely long-term outcomes for patients who stop treatment by two years."	Evidence in support of stopping rules is provided in CS B.3.3.6	The EAG is not aware of any additional evidence available from clinical trials or real-world studies but would be happy to receive and review any additional evidence during technical engagement.
Page 80. "For all IO therapies, a 2-year stopping rule was applied as clinical advice[10] to the company was that treatment would be discontinued for most patients at, or prior to, this timepoint."	Amend text: "For all IO therapies, a 2-year stopping rule was applied in line with the NICE Melanoma HEMR and previous appraisals in this indication, as well as clinical advice[10] to the company that treatment would be discontinued for most patients at, or prior to, this timepoint. This is also consistent with other clinical advice, both to the EAG, and in the NICE Melanoma HEMR: "In clinical practice, the committee	To clarify that stopping rules were applied according to precedent in addition to clinical opinion.	Text amended as follows (p81). "For all IO therapies, a 2-year stopping rule was applied in line with the NICE Melanoma HEMR and the clinical advice[10] given to the company that treatment would be discontinued for most patients at, or prior to, this timepoint."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	felt strongly that patients would not continue treatment beyond two years, based on their clinical experience…as clinician experience and confidence in treatment with these therapies has grown, they are happy to stop treatment at two years and can be sure of an ongoing immune response”..”		
Page 94. “The EAG removed the 2-year stopping rules for all IO therapies and amended the nivolumab + ipilimumab TTD data after [redacted] years to make the approach to modelling TTD more consistent with the approach used to model TTD for the other treatments.”	Amend text to read: “The EAG removed the 2-year stopping rules for all IO therapies and amended the nivolumab + ipilimumab TTD data after [redacted] years (the maximum observed follow-up for nivolumab+ipilimumab TTD data from CheckMate 067 in the model) to make the approach to modelling TTD more consistent with the approach used to model TTD for the other treatments.”	To improve accuracy of the document and provide context of the choice of cut-off point.	Text amended as follows (p94): “The EAG removed the 2-year stopping rules for all IO therapies and amended the nivolumab + ipilimumab TTD data after [redacted] years (the maximum observed follow-up for nivolumab+ipilimumab TTD data from CheckMate 067 in the model) to make the approach to modelling TTD more consistent with the approach used to model TTD for the other treatments.”
Page 102: “In the company base case, as clinical opinion[10] was that less than 10% of patients remain on	Amend text to read: "As clinical opinion was that less than 10% of patients remain on IO therapies after 2 years and in	Current text misleadingly implies that clinical opinion was the only reason for stopping rules to be	Text amended as follows (p103): “In the base case analysis, in accordance with the NICE Melanoma HEMR and as clinical

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
IO therapies after 2 years, the company implemented a 2-year treatment stopping rule for all IO therapies"	accordance with the NICE Melanoma HEMR (for which "the committee felt strongly that patients would not continue treatment beyond two years") and previous melanoma appraisals, the company implemented a 2-year treatment stopping rule for all IO therapies in the base-case analysis."	applied in the base case analysis.	opinion[10] was that less than 10% of patients remain on IO therapies after 2 years, the company implemented a 2-year treatment stopping rule for all IO therapies"
Page 102. "In addition, no stopping rules were specified in the NICE recommendations for nivolumab,[12] pembrolizumab[13] or nivolumab+ipilimumab[11] as treatments for advanced melanoma."	Either remove text, or add notes for the following: • That two-year stopping rules were included in the base case analyses that informed decision-making for all three appraisals and a two-year stopping rule was included in the NICE Melanoma HEMR. • That it is unusual for stopping rules to be specified in the NICE recommendations. For example the following nivolumab appraisals had stopping rules in trials but not recommendations: TA817, TA818, TA857, TA865. Similarly TA366 (Pembrolizumab for advanced melanoma not	To improve accuracy of the document and add context around the use and justification for using 2-year stopping rules.	This is not a factual inaccuracy. No change required.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	previously treated with ipilimumab) did not include a stopping rule in its recommendation (this is just a small set of examples, not intended to be exhaustive). • Add examples of where stopping rules are specified in the NICE recommendations		
Page 103, Table 45.	Clarify that proportions in the table are taken from K-M data and do not reflect the modelled TTD curves applied in the company model.		Table 45 amended as follows (p103): "Proportion of patients remaining on treatment at 2 years (K-M data)"
Page 103 "This means that all the patients who receive treatment with nivolumab at [redacted] years continue to receive nivolumab treatment for at least another [redacted]."	Amend text: "This means that all the patients who receive treatment with nivolumab at [redacted] years continue to receive nivolumab treatment until disease progression or death."	Current text misleadingly implies that people do not die or progress in-between the two time-points	Text amended as follows (p103): "This means that all the patients who receive treatment with nivolumab at [redacted] years continue to receive nivolumab treatment until disease progression or death."
Page 117. "The EAG revisions that had the biggest impact on cost	Amend text: "The EAG revisions that had the biggest impact on cost	To enhance objectivity of the text.	Text amended as follows: "The EAG revisions that had the biggest impact on cost

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
effectiveness results were removal of the 2-year treatment stopping rule (which also involved more appropriate modelling of TTD and AEs for patients treated with nivolumab+ipilimumab) and alternative costing of subsequent systemic therapies."	effectiveness results were removal of the 2-year treatment stopping rule (which also involved alternative modelling of TTD and AEs for patients treated with nivolumab+ipilimumab) and alternative costing of subsequent systemic therapies."		effectiveness results were removal of the 2-year treatment stopping rule (which the EAG considers also involved more appropriate modelling of TTD and AEs for patients treated with nivolumab+ipilimumab) and alternative costing of subsequent systemic therapies."

Issue 9 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19. Issue 12 summary table. "However, the company has applied nivolumab+ipilimumab AE costs and disutilities even when patients are only receiving nivolumab monotherapy."	Update text to read: "The company has applied evidence on rates of adverse events from long-term follow-up of the CheckMate 067 trial (minimum 60 months follow-up), which will include outcomes for patients after stopping ipilimumab."	Current text misleadingly implies that the company only used evidence on adverse events from the induction phase of the nivolumab + ipilimumab arm of CheckMate-067	This is not a factual inaccuracy. However, for clarity, the EAG has made the amendment suggested by the company. The EAG has also changed the issue heading to: "Inappropriate AE costs and disutilities applied for patients treated with nivolumab+ipilimumab" The EAG has also changed the response to 'What additional

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			evidence or analyses might help to resolve the issue' from 'None' to: "AE data for the induction and maintenance treatment periods of nivolumab+ipilimumab from the CheckMate 067 trial.
Page 94. Table 41. "Patients treated with nivolumab+ipilimumab only receive ipilimumab for three model cycles. However, the company has applied nivolumab+ipilimumab AE costs and disutilities even when patients have stopped receiving ipilimumab and are only receiving nivolumab monotherapy. The EAG has assumed that once treatment with ipilimumab has ceased, only the costs and disutilities associated with treatment with nivolumab are applied in the model."	Amend text to read: "Patients treated with nivolumab+ipilimumab only receive ipilimumab for three model cycles. The company has applied evidence on rates of adverse events from long-term follow-up of the CheckMate 067 trial (minimum 60 months follow-up), which will include outcomes for patients after stopping ipilimumab. The EAG has assumed that once treatment with ipilimumab has ceased, only the costs and disutilities associated with treatment with nivolumab are applied in the model."	Current text misleadingly implies that the company only used evidence on adverse events from the induction phase of the nivolumab + ipilimumab arm of CheckMate-067.	This is not a factual inaccuracy. However, for clarity, the EAG has made the changes suggested by the company.
Page 106:	Add note that AE rates were obtained from the 60-month	Current text misleadingly implies that the company only used	This is not a factual inaccuracy. However, for clarity, the EAG has

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“However, the company has applied the same AE costs and disutilities associated with nivolumab+ipilimumab irrespective of whether the patient is receiving nivolumab+ipilimumab (four treatment cycles) or nivolumab monotherapy (until disease progression or death). The EAG considers that whilst there may be some residual adverse effects from having been treated with ipilimumab, it is more appropriate to only apply the AE costs and disutilities associated with nivolumab monotherapy once treatment with ipilimumab has stopped.”	follow-up of CheckMate-067 which includes both the induction (nivolumab + ipilimumab) phase and the monotherapy phase.	evidence on adverse events from the induction phase of the nivolumab + ipilimumab arm of CheckMate-067.	added the extra information suggested by the company. “However, the company has applied the same AE costs and disutilities associated with nivolumab+ipilimumab (incidence rates sourced from CheckMate 067 trial 60-month follow-up data) irrespective of whether the patient is receiving nivolumab+ipilimumab (four treatment cycles) or nivolumab monotherapy (until disease progression or death).”

Issue 10 Modelling errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
ID1688 Nivolumab-relatlimab EAG Model v0.1 22.06.23 [ACIC]. Sheets: NIVO-RELA; NIVO; NIVO+IPI; PEM. Columns AV:AW. Rows 18:677	General population utilities should be age-adjusted when applied for each comparator. For example in cell 'NIVO-RELA'!AV18 =AQ18*IF(AND('EAG Revisions'!$D$13=1,$M18>=BB$6),INDEX('Life Tables'!$AE$14:$AF$2102,**$M18**,2),$AU18*AV$6)	To enhance accuracy of the modelling amendment.	Thank you for highlighting this error. The error (R11) has been corrected in the updated model (ID1688 Nivolumab-relatlimab EAG Model v3 17 July 2023 [ACIC].xlsb) and updated results have been provided in the EAG report, Table B, Table C, Table D, Table 50, Table 52 and Table 54.
ID1688 Nivolumab-relatlimab EAG Model v0.1 22.06.23 [ACIC]. Sheet OS Data. Cell V132.	Amend label to "adjusted ITC (OS) vs niv_rela"	To correct label.	Thank you for highlighting this error. Label corrected (see file ID1688 Nivolumab-relatlimab EAG Model Revisions Data 17 July 2023 [ACIC].xlsx).
ID1688 Nivolumab-relatlimab EAG Model v0.1 22.06.23 [ACIC]. Sheet NIVO+IPI. Cell AZ17.	This incorrectly has a formula in it, it should be blank. Note that this will in turn affect all results for cost-effectiveness	Correct error in model and check reporting of results in report.	Thank you for highlighting this error. The error (R4) has been corrected in the updated model (ID1688 Nivolumab-relatlimab EAG Model v3 17 July 2023 [ACIC].xlsb) and results for

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	comparisons against nivolumab+ipilimumab. Hence the EAG needs to check, and if appropriate amend, all results presented in their report for Table C and Tables 52, 53, 56, 57, 58 and accompanying text.		comparisons against nivolumab+ipilimumab updated in the EAG report, Table C, Table 52 and Table 53.
ID1688 Nivolumab-relatlimab EAG Model Revisions Data v2.0 30.06.2023 [ACIC]	Upon loading an error occurs when trying to update links: "We can't update some of the links in your workbook right now" Please check and remove this source of error	Check and remove source of error	Thank you for highlighting this error. The source of the error has been removed from the spreadsheet.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 29.	Health state utilities estimated from RELATIVITY-047 are not publicly available and should be marked academic in	PF health state utility: [redacted] PD health state utility: [redacted]	Thank you for highlighting this error. AIC marking added.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	confidence.		
Page 86.	BRAF status of RELATIVITY-047 trial patients is not publicly available and should be marked academic in confidence.	The subsequent treatment distributions in Table 34 correspond to the proportions of RELATIVITY-047 trial patients with BRAF-mutant ([redacted]) or BRAF-wild type tumours ([redacted]).	Thank you for highlighting this error. AIC marking added.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 5.1.1-2. Figure 2, Figure 3,	These data are not publicly available and may enable back calculation of confidential discounts.		Thank you for highlighting this error. CIC marking added.
Section 6.3.1. page 98.	These data are not publicly available and should be marked	There is substantial right censoring after [redacted] (RELATIVITY-047 trial minimum trial follow-up),	Thank you for highlighting this error. AIC marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	academic in confidence.		added.
Section 6.3.1. page 99. Figure 6.	These data are not publicly available and should be marked academic in confidence.	[redacted]	Thank you for highlighting this error. AIC marking added.
Section 6.6.1. page 104.	These data are not publicly available and should be marked academic in confidence.	The company did not use RELATIVITY-047 trial data to model subsequent treatments as follow-up data were too short to provide reliable estimates (median follow-up=[redacted] months).	Thank you for highlighting this error. AIC marking added.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma ID1688

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **16 August 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bristol Myers Squibb
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**NA**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**NA**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Lack of clinical trial evidence for patients aged 12 to 18 years (EAG report 2.2.3, 2.3.2, 3.1 and 3.8)	No	The company acknowledges that no clinical data are available to support the efficacy or safety of nivolumab-relatlimab in patients aged 12 to 18 years. Although rare, melanoma in adolescents behaves similarly to the disease in adults, and the treatment of adolescents and adults with immune checkpoint inhibitors, including nivolumab + relatlimab, is expected to have an equivalent risk-benefit profile to adults. Rationale for the extrapolating the benefit of adults to adolescents is outlined in the Opdualag EPAR[1], as also provided in the EAG clarification questions. *"No adolescents were included in the clinical studies. Given the similarity of disease histology, genetic background, treatment and prognosis of metastatic melanoma for adults and adolescents, and sufficiently comparable predicted drug exposure in adults and adolescents, based on popPK simulations in patients weighing at least 30 kg, extrapolation of efficacy and safety from adults to the adolescent population is considered acceptable. In these simulations, both the situation of a reduced clearance and volume of distribution of relatlimab and nivolumab, as well as the situation of a comparable clearance and volume of distribution in adolescents and adults, was simulated. In both cases the exposure is considered sufficiently comparable between adolescent and adult patients.*

		Therefore, inclusion of adolescents 12 years of age and older in the indication is considered approvable. *The available safety data of nivolumab in adolescents, indicate a comparable short term safety profile for adolescents as for adults. Given that nivolumab and relatlimab are both check-point inhibitors, also for relatlimab a comparable short term safety profile for adolescents and adults may be expected in case of comparable exposure. Long-term safety data are missing, especially the long-term effect of endocrine AEs might be different between adults and adolescents. Given the poor prognosis of adolescents with metastatic or unresectable (advanced melanoma), the uncertainty regarding the long-term toxicity profile is not considered a major concern. In addition, long-term safety will be followed - Assessment report EMA/720884/2022 Page 146/147 up post approval (cat 3 study)."* Although it is acknowledged there is no established NHS treatment pathway for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma, the NICE guidelines for the assessment and management of melanoma (NG14) states that "the committee agreed that treatment should not differ between children and adults, and that recommendations also apply to children and young people".[2]
Issue 2: Clinical effectiveness data are not available for patients for whom immune-oncology combination therapy is not suitable (EAG report 2.3.2, 3.7.1 and 3.8)	No	The company disagrees with the language provided in this issue as the NICE guidelines for the assessment and management of melanoma (NG14)[2] do not use "IO combination" terminology to describe suitability. The company recognises that nivolumab + ipilimumab and nivolumab-relatlimab are combinations of IO therapies; however, while nivolumab may be in both treatment combinations, the mechanisms of action of ipilimumab and relatlimab are different and thus the therapies are not interchangeable. The company welcomes clinical expert opinion for consideration to address this issue.

		Regarding immunotherapies, NG14[2] part 1.8.8 states, "Offer nivolumab plus ipilimumab to people with untreated stage IV or unresectable stage III melanoma if suitable for them based on the factors in recommendation 1.8.6. [2022]" and section 1.8.9 states, "If nivolumab plus ipilimumab is unsuitable or unacceptable (for example, because of potential toxicity), offer pembrolizumab or nivolumab monotherapy. [2022]". Section 1.8.6 of NG14 which determines suitability for nivolumab + ipilimumab, states "When choosing systemic anticancer treatment for untreated stage IV or unresectable stage III melanoma, base treatment decisions on the following factors: • comorbidities and performance status • risk of treatment toxicity • whether potential treatment toxicity will be tolerated • presence of symptomatic brain metastases • tumour biology (for example, high disease burden, rapid progression, lactate dehydrogenase level). Treatment decisions should be made after a full assessment of the risks and benefits by the treating oncologist and discussion with the person, in line with NICE's guideline on shared decision making." Furthermore, recent consultation with clinicians has confirmed that the choice between the available IO treatments is individualised and ultimately based on its suitability for the patient. On consultation, UK clinicians expressed the opinion that nivolumab-relatlimab may also be a good alternative in patients either unfit to receive nivolumab + ipilimumab, or in centres without the capacity or experience to manage potential toxicities that arise from treatment with nivolumab + ipilimumab. Therefore, clinicians anticipated nivolumab-relatlimab to be used initially in patients who are currently receiving IO monotherapy.[3] The company appreciate that

		patients eligible for nivolumab-relatlimab may also be considered suitable for nivolumab + ipilimumab; however, many patients in NHS clinical practice are not suitable for nivolumab + ipilimumab and receive nivolumab or pembrolizumab monotherapy. However , as nivolumab-relatlimab has demonstrated similar clinical effectiveness to nivolumab + ipilimumab, but with a better safety profile, a comparison between nivolumab-relatlimab is also of relevance. The EAG report (2.3.2) states "It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial and CheckMate 069 trial) should be used to inform decision-making for the population for whom nivolumab + ipilimumab is not suitable as these trials only recruited patients for whom IO combination therapy was considered suitable." The company wish to note that the suitability criteria for eligibility for nivolumab + ipilimumab per NG14 were developed after the CheckMate 067 trial. Therefore, patients who met the inclusion/exclusion criteria for RELATIVITY-047 were clinically suitable for nivolumab + ipilimumab, however given that the study started in 2018 and NICE approval for nivolumab + ipilimumab was in 2016, it is plausible that in practice patients would have not enrolled in RELATIVITY-047 and instead received nivolumab + ipilimumab. Of note, the patient populations enrolled into the RELATIVITY-047 and CheckMate-067 trials were highly similar. This is demonstrated through similarities in the eligibility criteria for trial enrolment, as presented in Table 1, and similar baseline demographics and disease characteristics of patients enrolled in RELATIVITY-047 and CheckMate-067, as demonstrated by the small standard mean difference values presented in Table 2. The baseline demographics and disease characteristics for the nivolumab arms of RELATIVITY-047 and CheckMate-067 are presented in the CS, Appendix D.4.2.4.2. Minimal differences were also seen between the nivolumab arms of the trials. In addition, it is noted that comparative clinical effectiveness for nivolumab-relatlimab versus nivolumab comes from the randomised, double-blind RELATIVITY-047 trial. There is no evidence to suggest that eligibility for

nivolumab + ipilimumab would act as a treatment-effect modifier when estimating relative effectiveness.

Table 1: Key eligibility criteria for patients enrolled in RELATIVITY-047 and CheckMate-067

	RELATIVITY-047	CheckMate-067
Inclusion criteria	• Histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the 8th edition of the AJCC staging system • No prior systemic anti-cancer therapy for unresectable or metastatic melanoma, but prior adjuvant or neoadjuvant melanoma therapy with a specified regimen was allowed (anti-PD-1, anti-CTLA-4, or BRAF-MEK containing regimen if ≥ 6 months between last dose and date of	• Histologically confirmed stage III (unresectable) or stage IV melanoma • No prior systemic treatment for advanced disease (i.e. no prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) • Males and females ≥ 18 years of age

			recurrence; interferon with last dose ≥ 6 weeks before randomisation) • Males and females ≥ 12 years of age • ECOG performance status of 0 or 1, or a Lansky performance score ≥ 80% for minors • Known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period	• ECOG performance status of 0 or 1 • Known BRAF V600 mutation status	
		Exclusion criteria	• Active or untreated brain or leptomeningeal metastases • Uveal melanoma • Active autoimmune disease or condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone	• Active brain metastases or leptomeningeal metastases. Patients with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after	

			equivalent) or other immunosuppressive medications within 14 days of start of study treatment • History of myocarditis	treatment is complete and within 28 days prior to first dose of study drug administration • Ocular melanoma • Patients with active, known or suspected autoimmune disease • Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration

Table 2: Baseline characteristics for patients in the nivolumab-relatlimab arm of RELATIVITY-047 and nivolumab + ipilimumab arm of CheckMate-067

	Nivolumab-relatlimab (n = 349)	Nivolumab + ipilimumab (n = 307)	SMD
Demographics			
Age (years)			[redacted]
Mean ± SD	61.22 ± 13.98	59.50 ± 13.63	
Sex, %			[redacted]
Male	205 (58.74)	201 (65.47)	
Female	144 (41.26)	106 (34.53)	
Race, %			[redacted]
White	336 (96.28)	303 (98.70)	
Non-White	7 (2.01)	4 (1.30)	
Missing / N	6 / 349 (1.72)	0 / 307 (0.00)	
Geographic region, %			[redacted]
Rest of World	312 (89.40)	246 (80.13)	
USA	37 (10.60)	61 (19.87)	

		History of smoking, %			[redacted]	
		Never smoked	211 (60.46)	156 (50.81)		
		Current/former	123 (35.24)	137 (44.63)		
		Missing / N (%)	15 / 349 (4.30)	14 / 307 (4.56)		
		Disease characteristics				
		Time from advanced melanoma diagnosis until randomization (years)			[redacted]	
		Mean ± SD	2.85 ± 4.85	3.57 ± 4.48		
		Prior adjuvant therapy, %			[redacted]	
		Not received	315 (90.26)	236 (76.87)		
		Received	34 (9.74)	71 (23.13)		
		AJCC M stage with LDH category 1, %			[redacted]	
		M0/M1any[0]	230 (65.90)	197 (64.17)		
		M1any[1]	119 (34.10)	110 (35.83)		
		AJCC disease stage, %			[redacted]	
		Stage III	35 (10.03)	16 (5.21)		
		Stage IV	314 (89.97)	291 (94.79)		
		Melanoma subtype, %			[redacted]	
		Cutaneous acral	39 (11.17)	11 (3.58)		

		Cutaneous non-acral	245 (70.20)	242 (78.83)	
		Mucosal	23 (6.59)	27 (8.79)	
		Other	42 (12.03)	27 (8.79)	
		History of brain metastases, %			[redacted]
		No history of brain metastases	342 (97.99)	297 (96.74)	
		History of brain metastases	7 (2.01)	10 (3.26)	
		ECOG performance status, %			[redacted]
		≥ 1	116 (33.24)	83 (27.04)	
		0	233 (66.76)	224 (72.96)	
		BRAF mutation status, %			[redacted]
		Mutation Wild type	216 (61.89)	206 (67.10)	
		Mutation positive	133 (38.11)	101 (32.90)	
		LDH category 1, %			[redacted]
		≤ ULN	223 (63.90)	194 (63.19)	
		> ULN	126 (36.10)	113 (36.81)	
		LDH category 2, %			[redacted]
		> 2 X ULN	31 (8.88)	36 (11.73)	
		≤ 2 X ULN	318 (91.12)	271 (88.27)	

		<table><tr><td>PD-L1 expression category, %</td><td></td><td></td><td>[redacted]</td></tr><tr><td>< 1%/non-quantifiable</td><td>205 (58.74)</td><td>152 (49.51)</td><td></td></tr><tr><td>≥ 1%</td><td>144 (41.26)</td><td>155 (50.49)</td><td></td></tr></table> Furthermore, as an internal validation of the adjusted ITC between nivolumab-relatlimab and nivolumab + ipilimumab, the weighted nivolumab arms from both trials were compared for all safety and efficacy outcomes. An analysis using investigator-assessed PFS showed a similar hazard of progression or death for both nivolumab arms after weighting (HR [redacted], 95% CI: [redacted], [redacted]), with the point estimate of the HR close to 1 and the CI spanning 1. An analysis of OS showed a similar risk of mortality for both nivolumab arms after weighting (HR [redacted], 95% CI: [redacted], [redacted]), with the point estimate of the HR close to 1 and the CI spanning 1. This analysis therefore demonstrated that after weighting there were no differences in PFS and OS outcomes between the nivolumab arm of CheckMate-067 and the nivolumab arm of RELATIVITY-047. These similarities collectively demonstrate that, although RELATIVITY-047 may plausibly provide evidence on patients who would not be treated with nivolumab + ipilimumab, the similarity of outcomes for patients treated with nivolumab in both trials, further supports their similarity.
Issue 3: Both investigator-assessed and blinded independent central review (BICR)-assessed progression-free survival (PFS) data used in network meta-analyses (NMA; EAG report 3.4.1, 3.7.1, 3.7.3 and 3.8)	No	Of the two measures for assessing disease progression, the company retains that BICR is the preferred measure. This is for the reasons outlined in the response to clarifications and briefly summarised below: • The assessment of nivolumab-relatlimab should utilise PFS per BICR to inform estimates as this is the primary study endpoint in RELATIVITY-047 for which the trial was appropriately powered. PFS per investigator-assessment was an exploratory endpoint for which RELATIVITY-047 was not powered to demonstrate differences by treatment

		• PFS per BICR is referred to as the gold standard for disease progression as it is more objective than PFS per investigator-assessment.[4] This view is well advocated by EMA and FDA guidance[5, 6] • BICR is favoured as it removes assessment bias between readers, reduces variability and increases accuracy in determining if a patient has progressed, thus counteracting many issues that can often arise from investigator-assessment a point acknowledged by the EAG in their report; Section 3.4.1 "The EAG agrees with the company that the use of BICR for the objective assessment of radiological outcomes can reduce the risk of systematic investigator bias which may favour one treatment arm"
Issue 4: Uncertainties around fractional polynomial (FP) NMA model selection to estimate time-varying hazard ratios (HR; EAG report 3.7.3 and 3.8)	No	The company agrees with the EAG that clinical plausibility is very important when choosing a statistical model. This is why the clinical plausibility of the four best-fitting models (based on deviance information criterion [DIC]) was used to inform the choice of model (CS B.3.3.2 and response to EAG CQ A10). All extrapolations of time-to-event data in the model were performed and selected following statistical best-practice as outlined in the NICE TSDs 14 and 21.[7, 8] Models were therefore selected based on: - Assessment of proportional hazards - Visual fit to the observed KM data within trial periods - Assessment of the underlying hazard functions - Statistical goodness of fit (based on AIC, BIC or DIC as appropriate) - Validation by clinicians with experience of treating unresectable or metastatic melanoma It is further noted that clinical plausibility relates to both good within-sample fit and plausible extrapolations. Model fit statistics (such as the DIC) provide information

		on the former and so form an important part of assessing clinical plausibility; models with poor within-sample fit are unlikely to be clinically plausible.
Issue 5: Difficulties interpreting PFS and overall survival (OS) FP NMA results (EAG report 3.7.3, 3.7.4 and 3.8)	No	In their report the EAG states that it "…considers that it is not appropriate to infer statistical significance (or lack of) from the FP NMAs 95% CrIs" The company notes that deterministic estimates of cost-effectiveness are based on point estimates, whilst probabilistic estimates of cost-effectiveness (including estimates of uncertainty) are derived via Monte Carlo sampling. As such, inferences around statistical significance will not impact on decision-making. The company acknowledges that there are strengths and limitations with each of the approaches to performing indirect comparisons (FP NMA, constant HR NMA, adjusted ITC). The company acknowledges that the EAG approach to estimating OS and PFS may also be used for decision-making: • nivolumab-relatlimab versus nivolumab: RELATIVITY-047 trial • nivolumab-relatlimab versus nivolumab + ipilimumab: adjusted ITCs • nivolumab-relatlimab versus pembrolizumab: EAG constant HR NMAs
Issue 6: Clinical effectiveness of nivolumab-relatlimab versus pembrolizumab: data limitations (EAG report 2.3.4, 3.7.1, 3.7.3 and 3.8)	No	The company notes that decision-making should make best use of the available evidence. For the indirect comparison of nivolumab-relatlimab versus pembrolizumab there is evidence on effectiveness outcomes over time from two large, well-conducted trials: RELATIVITY-047 and KEYNOTE-006.
Issue 7: Limited generalisability of company cost effectiveness results to NHS patients for whom immune-oncology combination therapy is	No	The company reiterate that NG14 refers to "nivolumab + ipilimumab" suitability and not as "IO combination". The relevance of clinical effectiveness data to NHS patients for whom nivolumab + ipilimumab is not suitable is described in detail in

not suitable (EAG report 6.1 and 6.11)		issue 2. Key points pertinent to the cost-effectiveness results are summarised here. • The company recognises that nivolumab + ipilimumab and nivolumab-relatlimab are combinations of IO therapies; however, the therapies are not interchangeable. • If patients who met the inclusion/exclusion criteria for RELATIVITY-047 were clinically suitable for nivolumab + ipilimumab, it is plausible that they would have not enrolled in RELATIVITY-047 and instead received nivolumab + ipilimumab. The company welcomes clinical expert opinion for consideration to address this issue. • Consultation with clinicians has confirmed that the choice between the available IO treatments is individualised and ultimately based on suitability of the patient. Nivolumab-relatlimab may be used initially in patients who are currently receiving IO monotherapy.
Issue 8: Uncertain RELATIVITY-047 trial long-term OS data (EAG report 6.2, 6.3 and 6.11)	No	The company acknowledges that there is uncertainty regarding long-term OS extrapolations for nivolumab-relatlimab used in the cost-effectiveness model. However, the OS data from RELATIVITY-047 provided in this submission is the best available evidence for nivolumab-relatlimab in this indication. The EAG noted that they were not able to provide more reliable OS extrapolations based on the latest data cut from RELATIVITY-047 (EAG Report 6.3.2). The company also notes that the three evidence sources deemed by the EAG to be the best available for estimating OS (listed in Issue 5) each demonstrates an OS benefit for nivolumab-relatlimab (against nivolumab, nivolumab + ipilimumab and pembrolizumab). The company accepts that there is uncertainty around the long-term OS hazards, however extrapolations were chosen based on NICE DSU TSD 14 and 21 guidance, including validation by clinicians with experience of treating advanced melanoma patients in England (CS B.3.3.2). Clinicians advised that, given that

<table>
<tr><td></td><td></td><td>nivolumab-relatlimab features nivolumab in combination, there was no reason to think it would not demonstrate similar long-term survival profiles to the other IOs.

The NMA performed by the company resulted in a constant HR against nivolumab + ipilimumab of 0.96 (95% confidence interval 0.72, 1.27) indicating an OS advantage for nivolumab-relatlimab. Time-varying HRs from the same NMA showed nivolumab-relatlimab was associated with a numerical advantage in OS in comparison with nivolumab + ipilimumab at month 3 (0.84 [0.56, 1.26]) to month 12 (0.88 [0.72, 1.35]), performed similarly at month 18 (1 [0.72, 1.40]) and was associated with a slight numerical disadvantage from month 24 (1.01 [0.72, 1.43]) to month 48 (1.02 [0.72, 1.47]). The OS HR after weighting from the company's adjusted ITC is 0.94 (0.74, 1.19), again indicating a slight advantage for nivolumab-relatlimab.

We do not believe any further analyses can be provided to improve the existing approach, therefore the company maintains its preferred approach to modelling OS used in the company base-case.</td></tr>
<tr><td>Issue 9: Implausible proportions of patients reaching background mortality after progression (nivolumab-relatlimab versus nivolumab + ipilimumab and versus pembrolizumab; EAG report 6.2, 6.3 and 6.11)</td><td>Yes</td><td>The company believes that when considering estimates of post-progression survival, it is more informative to consider estimates taken from the same time-point.

Observed data for immunotherapies in this indication (nivolumab, nivolumab + ipilimumab, ipilimumab in CheckMate-067; pembrolizumab, ipilimumab in KEYNOTE -006) show that there are still divergences in observed long-term PFS and OS indicating that there may be up to 15% of patients alive after disease progression at 84 to 90 months (Table 3 and Table 4).
Table 3: 90-month survival outcomes CheckMate-067

<table>
<tr><th>Treatment arm</th><th>PFS at 90 months</th><th>OS at 90 months</th></tr>
</table>
</td></tr>
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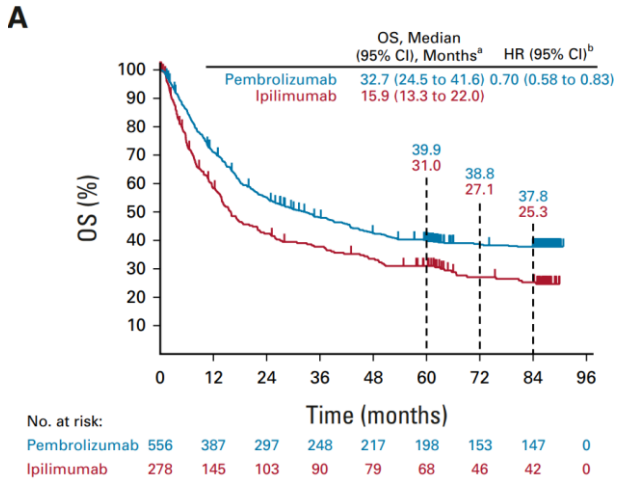
		<table><tr><td>Nivolumab + ipilimumab</td><td>48%</td><td>33%</td></tr><tr><td>Nivolumab</td><td>42%</td><td>27%</td></tr><tr><td>Ipilimumab</td><td>22%</td><td>7%</td></tr><tr><td colspan="3">Adapted from Figure 2 of Hodi et al. 2022.[9]</td></tr></table> **Table 4: 84-month survival outcomes from KEYNOTE -006** <table><tr><th>Treatment arm</th><th>mPFS at 84 months</th><th>OS at 84 months</th></tr><tr><td>Pembrolizumab</td><td>26.8%</td><td>41.2%</td></tr><tr><td>Ipilimumab</td><td>15.9%</td><td>27.6%</td></tr><tr><td colspan="3">Adapted from Figure A2 of Robert et al, 2023.[10]</td></tr></table> Furthermore, as noted in the original submission, the company approach to modelling PFS is likely to underestimate long-term PFS for nivolumab-relatlimab as it fails to capture the plateau observed in the KM data. This leads to inflated estimates of the number of patients remaining in the progressed disease state. The observed differences in long-term OS and PFS (and hence also post-progression survival) between the two combination treatments (nivolumab-relatlimab and nivolumab-ipilimumab) are consistent with results of the adjusted indirect comparison, which demonstrate (based on point estimates) a slight increase in OS for nivolumab-relatlimab coupled with a slight decrease in PFS.
Issue 10: Uncertain pembrolizumab NMA results: consequences for cost effectiveness results (EAG report 6.4.2 and 6.11)	No	For both OS and PFS indirect comparisons using both time-varying and fixed hazard ratios were performed. For PFS the EAG also performed an additional fixed hazard ratio analysis using IA PFS. These analyses all collectively demonstrated superior outcomes for nivolumab-relatlimab versus pembrolizumab for both OS and PFS.

		Indirect comparisons also demonstrate that pembrolizumab provides inferior OS and PFS to nivolumab (EAG report, Table 20). As such, the company believes that the KEYNOTE-006 trial provides the best available evidence to inform the effectiveness of pembrolizumab.

Issue 11: A 2-year treatment stopping rule should not have been applied (EAG report 6.5)	Yes	The decision to include a 2-year stopping rule for all immunotherapies was based on clinical advice to the company, previous NICE appraisals in this indication and the NICE melanoma HEMR. The company would like to re-iterate that natural waning to general population mortality hazards is applied in the cost-effectiveness model (CS B.3.3.3, B.3.3.6). This is supported by long-term data from the CheckMate-067 trial which shows nivolumab + ipilimumab OS hazards reaching general population mortality at approximately 5 years[11], within the trial follow-up. As this natural waning effect is observed, there is no need to implement further exploratory waning in the model. Furthermore, clinical experts noted that for all treatment arms in the model if patients have not died or progressed at 3-5 years they would be unlikely to progress or die from melanoma[3]. As nivolumab-relatlimab includes nivolumab, clinical expert position was that any long-term outcomes would be similar to that observed for IOs; i.e. with a long-term plateau in survival. Of note, natural waning occurs for nivolumab-relatlimab before it occurs for any of the other treatments. Hence the treatment effect of nivolumab-relatlimab is waned more than the treatment effects of the other IOs. Clinical advice to the EAG (EAG report 6.5.2) was that treatment is usually discontinued at or before two years due to toxicity associated with immunotherapy treatment. Further clinical advice sought by the company during technical engagement confirmed this, consistently noting that stopping treatment at two years was extremely common, and in-line with Blueteq Approval Criteria.[12] The company welcomes further clinical expert opinion for consideration to address this issue. Whilst no stopping rules were specified in NICE recommendations for nivolumab, pembrolizumab and nivolumab + ipilimumab in this indication, it is unusual for stopping rules to be specified in NICE recommendations. For example, TA817, TA818, TA857 and TA865 included stopping rules in their pivotal trials but these

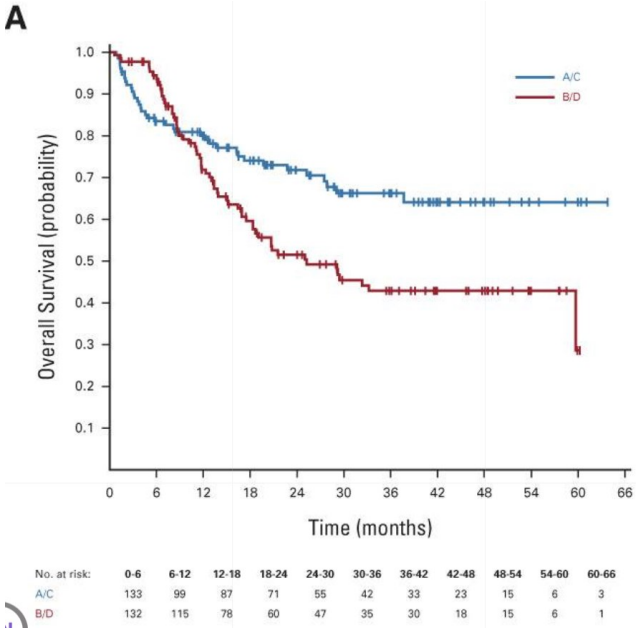
		were not specified in their respective recommendations. Due to their mechanisms of action, the clinical effect of IO therapies extends beyond a patient completing their treatment, providing long-term survivorship in a subset of patients. The company would like to re-iterate the existence of data, both from CheckMate-067[13], and real-world evidence[14] which demonstrate favourable long-term outcomes amongst patients who discontinued treatment with an immunotherapy prior to two years. This data was supported by UK clinicians based on their experience of using IO treatments in melanoma[3]. In addition, since the original company submission, seven-year follow-up from KEYNOTE-006 has been published[10]. In this study pembrolizumab was given for a maximum of two years, whilst ipilimumab was given for up to 12 weeks. Results, for both the overall and treatment naïve population, demonstrate both a persistent plateau in survival, and a persistent treatment effect for pembrolizumab (Figure 1). These findings are further supported by pooled long-term findings from ipilimumab monotherapy studies: data from almost 2,000 patients with follow-up to ten years demonstrates a sustained plateau in OS.

Figure 1: Kaplan-Meier estimates of OS by randomized treatment in the overall Keynote-006 population[10]



Further, the DREAMseq trial (which compared nivolumab + ipilimumab with combination targeted therapy in treatment-naïve patients with unresectable advanced BRAF-mutant melanoma) included a maximum treatment duration for nivolumab + ipilimumab of 84 weeks[15]. Three-year overall survival for nivolumab + ipilimumab was 66.2%, with a clear plateau out to five years (this compares with a three-year overall of 58% for nivolumab + ipilimumab in CheckMate 067) (Figure 2).

Figure 2: Kaplan-Meier curve of OS for treatment sequences in DREAMseq[16]



Key: A/C, patients receiving nivolumab + ipilimumab followed by dabrafenib + trametinib, B/D, patients receiving dabrafenib + trametinib followed by nivolumab + ipilimumab

As noted in the company submission, the concept of long-term survivorship for IO melanoma treatments was consistently supported by UK clinicians, who saw no biological rationale for nivolumab-relatlimab acting differently given that nivolumab-relatlimab features nivolumab in combination .

The company therefore considers that a two-year stopping rule for the modelled treatments is consistent with UK clinical practice and all previous PD-L1 targeted treatment in melanoma, whilst appropriately accounting for the cost of all these treatments to the NHS. Further, the use of a two-year stopping rule does not

		impact on the long-term effectiveness of immunotherapy treatment in advanced melanoma.
Issue 12: Ipilimumab adverse event costs and disutilities applied after treatment with ipilimumab has stopped (EAG report 6.7)	Yes	The company agrees with the EAG that rates of adverse events may not be constant over-time, particularly for nivolumab + ipilimumab. However, it is noted that for nivolumab + ipilimumab the EAG approach uses average rates of adverse events (derived from the full trial follow-up) during the combination phase, followed by rates for nivolumab during the monotherapy phase. The company disagrees with the EAG's proposed approach as it is unlikely to reflect how rates of adverse events for nivolumab + ipilimumab change over time. Patients who receive nivolumab + ipilimumab and experience a TRAE during the combination phase may experience this due to nivolumab, due to ipilimumab, or due to the combination. The median onset of TRAEs in patients who receive nivolumab monotherapy and experience a TRAE is between 5 weeks (skin-related TRAEs) and 15 weeks (renal TRAEs).[17] Therefore, using the rates of AEs to inform disutility associated with nivolumab monotherapy (including the first three months of treatment) but applying this to the nivolumab + ipilimumab arm is likely to overestimate the adverse event disutility in the nivolumab + ipilimumab arm in favour of nivolumab-relatlimab. The company recognizes that the company base case may also have overestimated disutility due to AEs by assuming a constant rate. An alternative approach is to implement a one-off impact of adverse events on costs and utilities. For consistency, this approach is implemented for all treatments. This approach slightly reduces the ICER to nivolumab from [redacted] in the company base case to [redacted]. Nivolumab-relatlimab dominates nivolumab + ipilimumab and pembrolizumab in both approaches.

		In support of the one-off approach, it is noted that when comparing rates of adverse events between CheckMate 067 data cuts ('minimum 5-years follow-up'[13] and 'minimum 6.5-years follow-up'[18]) there were no additional treatment-related adverse events of any grade for either nivolumab + ipilimumab or ipilimumab, and only one additional adverse event for nivolumab.
Issue 13: Company subsequent treatment assumptions (EAG report 6.6 and 6.11)	Yes/No	The company's approach to modelling subsequent treatments was based on the approach employed in the NICE melanoma HEMR. In the company's base case the proportion of patients receiving subsequent treatment after discontinuing each treatment arm was taken from the NICE melanoma HEMR. The distribution of subsequent therapies combined the treatment rules cited in the NICE HEMR and the proportion of patients with BRAF mutant or BRAF wild-type cancer in RELATIVITY-047. When estimating the proportion of patients that receive subsequent therapy, the company agree with the EAG that rates of subsequent systemic therapy are more informative than overall rates of subsequent treatment. However, the company does not agree with the EAG that rates of subsequent treatment would be the same between nivolumab-relatlimab and nivolumab, nor does it agree that the proportion of subsequent treatments would be the same for the two treatments. Amongst the patients who received subsequent systemic treatment in RELATIVITY-047, the proportion who received ipilimumab second-line (either as monotherapy or in combination with nivolumab) was [redacted]% ([redacted] / [redacted]) for first-line nivolumab-relatlimab and [redacted]% ([redacted] / [redacted]) for nivolumab, a relative increase of 52%. This demonstrates that nivolumab-relatlimab and nivolumab cannot be assumed to result in the same distribution of subsequent treatments, particularly as with longer follow-up from RELATIVITY 047 the proportion of patients in the nivolumab arm who subsequently receive ipilimumab second line is expected to further increase.

		Based on clinical feedback to the company, rates of treatment-related toxicity first line will influence both the proportion of patients who receive subsequent systemic treatment along and the distribution of subsequent treatments offered (in particular, notable toxicity first line meant that use of ipilimumab second-line was unlikely). As noted in the company submission, in RELATIVITY-047 a larger proportion of patients discontinued therapy due to a TRAE (Grade 3+) in the nivolumab-relatlimab arm versus the nivolumab arm (increase of [redacted]%). Hence, given that 48% of patients receiving nivolumab first-line received a subsequent systemic treatment in CheckMate 067, the rate would be [redacted]% for nivolumab-relatlimab. Consultation with clinicians confirmed that, following first-line treatment with nivolumab-relatlimab, BRAF mutant patients would likely receive a targeted treatment second-line. This is aligned with the company and EAG approach for BRAF mutant patients, and the NICE melanoma HEMR. There was more variability in the approach taken for BRAF wild-type patients. Use of ipilimumab second-line would be influenced by the availability of clinical trials, with an estimated 20% to 40% of BRAF wild-type patients receiving ipilimumab, and the remainder undertaking a clinical trial. Given this uncertainty, for modelling purposes it is assumed that the high-point (40%) of BRAF wild-type patients who receive a second-line treatment receive ipilimumab. In the original submission, it was assumed, in accordance with the NICE melanoma HEMR, that the mean time on second-line treatment would be 8.81 and 7.77 months with 0% and 61.5% second-line ipilimumab use, respectively (actual duration of treatment was not linked to the individual treatments received). As the revised approach for nivolumab-relatlimab is approximately half-way between the original approaches, a mean duration of 8.29 months is used.

To summarise, this results in the following approach to modelling subsequent therapies:

Treatment	Patients receiving subsequent therapy (%)
Nivolumab-relatlimab	[redacted]
Nivolumab	48.00%
Nivolumab + ipilimumab	35.00%
Pembrolizumab	48.00%

Subsequent treatment	Distribution receiving each subsequent therapy after nivolumab-relatlimab	Justification
Dabrafenib + trametinib	19.26%	38.52% (equally split between dabrafenib + trametinib and encorafenib + binimetinib) corresponding to the proportion of BRAF-mutant patients in RELATIVITY-047
Encorafenib + binimetinib	19.26%	
Chemotherapy (dacarbazine) or clinical trials	36.89%	60% of the BRAF wild-type patients in RELATIVITY-047

		<table><tr><td>Ipilimumab</td><td>24.59%</td><td>40% of the BRAF wild-type patients in RELATIVITY-047</td></tr></table> This results in an increase in the ICER of nivolumab-relatlimab to nivolumab from the company base case at [redacted] to [redacted]. Nivolumab-relatlimab dominates nivolumab + ipilimumab and pembrolizumab in both approaches.
Issue 14 Nivolumab-relatlimab has an EU marketing authorisation that limits use to patients with PD-L1 tumour expression <1% (EAG report 2.2.2, 2.3.2, 2.3.6, 2.3.7 and 3.8)	No	The MHRA appraisal of nivolumab-relatlimab is currently ongoing, with the decision anticipated in [redacted]. The anticipated indication under appraisal, as per the draft MHRA label, states: [redacted][19] As the CS aligns to the anticipated indication, which also aligns to that of the RELATIVITY-047 trial, no further analyses are required at this stage.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Company base case following EAG clarification questions (including corrections to HCRU costs and severity modifier)	-		ICER to nivolumab: [redacted] (all stated ICERs are per QALY) ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates ICER to pembrolizumab: nivolumab-relatlimab dominates
Key issue 3: Both investigator-assessed and BICR-assessed PFS data used in NMAs Key issue 5: Difficulties interpreting PFS and OS FP NMA results	Comparison versus nivolumab: PFS based on BICR, uses separate piecewise models: KM (first 3 months) + Gompertz. Comparison vs nivolumab + ipilimumab using FP NMAs for both OS and PFS (using both BICR and IA)	Comparison versus nivolumab: PFS based on IA, uses separate piecewise models: KM (first 3 months) + Gompertz. Comparison vs nivolumab + ipilimumab: use of adjusted indirect comparison for OS and PFS by IA.	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)

	Comparison vs pembrolizumab using FP NMAs for both OS and PFS (using both BICR and IA)	Comparison vs pembrolizumab: Constant HRs taken from NMA for OS and PFS by IA	
Key issue 12: Inappropriate AE costs and disutilities applied for patients treated with nivolumab + ipilimumab	AE costs and disutilities applied on a per-cycle basis.	AE costs and disutilities applied as a one-off in the first cycle	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)
Key issue 13: Company subsequent treatment assumptions	The proportion of patients going on to receive subsequent therapies based on rates of subsequent treatment from CheckMate-067 for nivolumab and nivolumab + ipilimumab. Nivolumab-relatlimab assumed to be [redacted]% lower than nivolumab reflecting the difference in treatment discontinuations due to a TRAE (Grade 3+) in the RELATIVITY-047 trial. The distribution of patients to each subsequent therapy was based on the proportion of BRAF-mutant patients in RELATIVITY-047 and treatment rules used in the NICE melanoma HEMR.	The proportion of patients going on to receive subsequent therapies based on subsequent systemic therapies in CheckMate-067 for nivolumab and nivolumab + ipilimumab. Nivolumab-relatlimab assumed to be [redacted]% lower than nivolumab reflecting the difference in treatment discontinuations due to a TRAE (Grade 3+) in the RELATIVITY-047 trial. Based on clinical expert opinion, the distribution of subsequent treatments following fist-line nivolumab-relatlimab was assumed to be: targeted treatment for BRAF mutant patients (no change from before),	ICER to nivolumab[redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)

	Pembrolizumab assumed equal to nivolumab for both rates of and distribution of subsequent treatments.	ipilimumab for 40% of BRAF wild-type patients and clinical trials / chemotherapy for the remaining 60% Pembrolizumab assumed equal to nivolumab for both rates of and distribution of subsequent treatments.	
Treatment beyond progression (EAR 6.5.1)	Treatment duration capped at disease progression for all treatments.	Removed cap on treatment duration at progression.	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)
EAG revision to company IV administration costs (EAR 6.9)	SB14Z (weighted average of settings) for the first administrations of nivolumab-relatlimab, nivolumab, and pembrolizumab, and for the first four doses of nivolumab + ipilimumab. - £526.52 SB15Z (weighted average of settings) for all subsequent administrations. - £470.62	EAG's preferred input costs used. SB12Z (outpatient) for all doses of nivolumab-relatlimab, nivolumab, and pembrolizumab. - £281.11 SB14Z (outpatient) cost to estimate the administration cost of the first four doses of nivolumab + ipilimumab. - £342.66	ICER to nivolumab: [redacted]) ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)
Company's base case following technical engagement (or revised base case). Including	Incremental QALYs against nivolumab: [redacted]	Incremental costs against nivolumab[redacted]	ICER to nivolumab: [redacted]

the EAG preferred approach to modelling PFS for nivolumab-relatlimab and nivolumab; AEs applied as a one-off; subsequent treatment proportions and distributions for nivolumab-relatlimab modelled as halfway between nivolumab + ipilimumab and nivolumab; treatment beyond progression and changes to IV administration costs.	Incremental QALYs against nivolumab + ipilimumab: [redacted] Incremental QALYs against pembrolizumab: [redacted]	Incremental costs against nivolumab + ipilimumab: [redacted] Incremental costs against pembrolizumab: [redacted]	ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: Nivolumab-relatlimab dominates (no change)

Sensitivity analyses around revised base case

Table 5: Fully incremental probabilistic analysis of company's revised base case (1,000 iterations)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,695
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	Strictly Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	Strictly Dominated

Figure 3: Cost-effectiveness plane of company's revised base case

Figure 1: Cost-effectiveness acceptability curve of company's revised base case

Figure 5: Tornado diagram of the 10 most influential parameters on the ICER against nivolumab

Figure 6: Tornado diagram of the 10 most impactful parameters on the ICER to nivolumab + ipilimumab

Figure 7:Tornado diagram of the 10 most impactful parameters on the ICER to pembrolizumab

Figure 8: Tornado diagram of the most impactful scenarios on the ICER to nivolumab + ipilimumab

Figure 9: Tornado diagram of the most impactful scenarios on the ICER to nivolumab + ipilimumab

Figure 10: Tornado diagram of the most impactful scenarios on the ICER to pembrolizumab

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Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma ID1688

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (see table A in section 1.1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Treating unresectable or metastatic melanoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Heather Shaw
2. Name of organisation	University College London NHS Foundation Trust
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with unresectable or metastatic melanoma? ☐ A specialist in the clinical evidence base for unresectable or metastatic melanoma or the technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for unresectable or metastatic melanoma?	To cure the disease. If this is not possible – to attain the longest potential meaningful control of the disease with manageable side effects as a result of the therapy applied.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	As a minimum: control of the disease – i.e. no progression over time (months to years), or preferably – a reduction/complete remission of disease which is sustained in months to years, or indeed in perpetuity.
10. In your view, is there an unmet need for patients and healthcare professionals in unresectable or metastatic melanoma?	Yes – there are a proportion of patients who do not respond, or respond only temporarily, to currently available treatment options and require alternative strategies.
11. How is unresectable or metastatic melanoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are NICE guidelines for treatment of individuals with metastatic or unresectable melanoma in England and Wales. The pathway of care is generally well defined but there are choices at each stage of therapy selection which can reasonably differ between clinicians and individual patient cases dependent on the circumstances. The technology would provide an alternate choice for certain groups of patients in addition to those already available – and may be more suitable/more beneficial to those patients.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology is not very different from that already in use in current care. It is intended for secondary care in the hands of specialised healthcare professionals. Training with regard to the new agent would be required. – this would not be outside that expected for any new agent introduction.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	This technology could potentially offer a more effective therapy choice (wrt PFS with data thus far but reasonably could be reflected into OS for the future) for certain groups of patients than that currently available due to modalities of action of the new development.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA400 (nivolumab plus	

ipilimumab), TA384 (nivolumab), TA366 (pembrolizumab)?	
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Lack of clinical trial evidence for patients aged 12 to 18 years (EAG report sections 2.2.3, 2.3.2, 3.1 and 3.8) *Would you expect the outcomes in adults with untreated unresectable or metastatic melanoma to be generalisable to 12 to 18 year olds?*	Yes – melanoma tends to behave in a biologically similar way in patients of different ages allowing for disease biology differences between individuals. Patient numbers of this age group have been small in prior comparable studies due to low numbers of cases yet we use the drugs currently licensed/available to good and comparable effect in this patient group when required – although the condition is thankfully rare in paediatric/TYA patients. It is reasonable to expect this technology to be similar. This patient population is often marginalised due to low numbers of cases and lack of trial enrolment or enrolment in numbers which are not statistically relevant. It would be unreasonable to exclude on this basis given the above on disease biology/behaviour and response.
Issue 2: Clinical effectiveness data are not available for patients for whom immune-oncology (IO) combination	Although the trial required that patients be considered suitable for ipi/nivo – with the results of the study in hand – there are groups of patients for whom the combination of nivo/rela may be suitable for whom ipi/nivo would not be. This rests mainly on the

therapy is not suitable (EAG report sections 2.3.2, 3.7.1 and 3.8) *Do you think there are people with untreated unresectable or metastatic melanoma who cannot have nivolumab plus ipilimumab who could have nivolumab–relatlimab?* *The available trial evidence is only in people who could have nivolumab plus ipilimumab. Is it generalisable to people who cannot?*	consideration of co-morbidities and potential for signficant immune related adverse events. The nivo/rela combination could/would be considered in those who may otherwise only have had single agent therapy and the study results suggest that offers better PFS and the potential for better OS as a result although that data is as yet immature.
Issue 3: Using both investigator-assessed and blinded independent central review (BICR)-assessed progression-free survival (PFS) data in network meta-analyses (NMA) (EAG report sections 3.4.1, 3.7.1, 3.7.3 and 3.8) *The company's NMA use BICR-assessed PFS data from the main trial (RELATIVITY-047) and investigator-assessed PFS from the other 3 trials. What is your view on this?*	These should reflect the same origin of data for comparison. BICR is not available for the other studies as far as I am aware therefore IA PFS would be more appropriate – I understand this point may already have been accepted.
Issue 4: Uncertainties around fractional polynomial (FP) NMA model selection to estimate time-varying hazard ratios (HR) (EAG report sections 3.7.3 and 3.8) *Do the results in the company submission in section B.2.9.1.2.1 appear clinically plausible to you?*	

Issue 5: Difficulties interpreting PFS and overall survival (OS) FP NMA results *Do the results in X appear clinically plausible to you?*	Not sure where X is meant to refer to – apologies!
Issue 6: Clinical effectiveness of nivolumab-relatlimab versus pembrolizumab: data limitations (EAG report sections 2.3.4, 3.7.1, 3.7.3 and 3.8) *How would you expect pembrolizumab to compare with nivolumab–relatlimab in terms of clinical effectiveness?*	One would expect – being aware of the clinically comparable mode of action/ORR/AE of pembrolizumab and nivolumab – for these two therapies to have performed similarly. Therefore one can reasonably assume that nivo/rela would perform better with regard to PFS vs pembrolizumab as it did with nivolumab.
Issue 7: Limited generalisability of company cost effectiveness results to NHS patients for whom IO combination therapy is not suitable (EAG report sections 6.1 and 6.11) *What proportion of people who cannot have nivolumab plus ipilimumab would be eligible for nivolumab–relatlimab, if any?*	As per prior answer – there are groups of patients with particular co-morbidities (such as inflammatory bowel disease) who could be considered for nivo/rela who would not routinely be suitable for nivo-ipi due to the AE profile which is now available for both combinations. There may also be patient preference for the apparently less cumbersome AE spectrum from nivo/rela vs nivo-ipi which reflects on QoL while on therapy (and afterward if the AE is not immediately resolved).
Issue 8: Uncertain RELATIVITY-047 trial long-term OS data (EAG report 6.2, 6.3 and 6.11) *Is it clinically plausible that people who have nivolumab–relatlimab could have longer OS than nivolumab plus ipilimumab, nivolumab or pembrolizumab?*	It is clinically plausible that there may be longer OS than nivo or pembro given it outperforms this class of drug in PFS as a starting position and we are aware that this is often reflected in OS data when it becomes available (per CM-067 etc). At this point is impossible to predict whether OS would be better than nivo-ipi given that this is not the comparator and much longer follow up is available for that combination.

Issue 9: Implausible proportions of patients reaching background mortality after progression (nivolumab-relatlimab versus nivolumab plus ipilimumab and versus pembrolizumab) EAG report sections 6.2, 6.3 and 6.11 *Are the proportions of people who are 'cured' (that is, have the same risk of death as the general population) after having the different treatments in table 42 plausible?*	Unclear why the proportion for second line cure would be better for nivo/rela vs others – although this may be modelled partly on exposure to ipi and its ORR subsequently given this patient population may be suitable for single agent (although may not have been for dual given the AE rate). There may also be a proportion of single agent anti PD1 patients who fall into this group although likely fewer….
Issue 10: Uncertain pembrolizumab NMA results: consequences for cost effectiveness results (EAG report sections 6.4.2 and 6.11) *Are the clinical effectiveness and safety profiles of pembrolizumab and nivolumab similar?*	Yes. Per prior points – clinically we would consider these therapies interchangeable for effectiveness and safety profiles.
Issue 11: A 2-year treatment stopping rule should not have been applied (EAG report section 6.5) *Do people continue on combination immunotherapies for longer than 2 years and if so what proportion and for how long?*	We would consider stopping therapy for all patients on immunotherapy at the two year point. Long term data from CM-067 and KN-006 suggests that a proportion of patients (particularly those who have achieved CR or maintained PR) do not require ongoing therapy to retain a long term response/cure of their disease. Ongoing therapy simply exposes these patients to risk of AE development over time, unnecessary hospital visits, blood tests and outpatient appointments. It is possible (and indeed likely) that stopping prior to two years for some patients would also be appropriate but the time point is currently driven by NHSE "rules" over re-treatment options. We are aware that many patients who have a response and have to stop early due to AE do not relapse and therefore this strengthens the position from a real world point of view.

	There are a small number of patients who are felt to require ongoing therapy with immunotherapy – those who have ongoing active disease at the two year point but maintain control (eg partial response or stable disease) on CPI, those who have relapsed following a prior cessation of therapy at two year point (current rules allow rechallenge to recapture response) – we would not routinely stop these patients again unless there is another reason to do so e.g. AE or patient wish or new data.
Issue 12: Ipilimumab adverse event costs and disutilities applied after treatment with ipilimumab has stopped (EAG report section 6.7) *Is it reasonable to assume that once treatment with ipilimumab stops, only costs and disutilities associated with nivolumab should be applied?*	As long as AE felt to be related to ipi or the combination of therapy have been resolved – then yes, reasonable that costs associated with nivo only are applied.
Issue 13: Company subsequent treatment assumptions (EAG report sections 6.6 and 6.11) *What treatments do people have when they finish first-line treatment for unresectable or metastatic melanoma and in what proportions?*	Given data thus far from KN006 and CM067 – there are a proportion of patients on both combination and single agent therapy who will not need further treatment as the immunotherapy they have received to date will maintain a response in perpetuity. This is a somewhat difficult question to be precise over otherwise given that it depends on individual patient characteristics, clinical trial availability at the time of progression and patient wishes. We would usually consider a clinical trial for all patients as first choice if a suitable study is available and patient eligible/wishes to be considered. Otherwise or if unsuitable/not wishing study: for those who are mutant and who have received ipilimumab – they would be offered BRAF/MEK directed therapy. For those who have not had ipi – they may be offered this a single agent either before or after BRAF/MEKi dependent on circumstances. For those who do not carry a relevant BRAF mutation – they would be offered ipi as a single agent if appropriate (not all patients are fit enough or would accept the potential

	benefit vs AE profile of the drug). In rare instances when either all of the above are either unsuitable or have resulted in PD – then we may offer chemotherapy (DTIC generally) to a selected subset of patients. The number of patients in this last category is very small. There are some patients for whom no second line treatment is appropriate or acceptable and will therefore have no subsequent therapy but best supportive care.
Issue 14: Nivolumab-relatlimab has an EU marketing authorisation that limits use to patients with PD-L1 tumour expression <1% (EAG report sections 2.2.2, 2.3.2, 2.3.6, 2.3.7 and 3.8) *Are outcomes in unresectable or metastatic melanoma affected by the level of PD-L1 tumour expression?*	PD-L1 is not routinely tested in the UK in melanoma as its value as a predictive biomarker in melanoma is limited. We know that patients who do not express this marker can benefit significantly from immunotherapy and would therefore exclude patients from meaningful treatment options if we applied cutoffs for PD-L1 expression. If this caveat were to be applied in the UK it would mean requiring funding/pathology time and an understanding of application of a test which is suboptimal for decision making in the disease type with this type of treatment. This would be inappropriate and would not be recommended clinically.
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab–relatlimab for untreated unresectable or metastatic melanoma ID1688

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with unresectable or metastatic melanoma or caring for a patient with unresectable or metastatic melanoma. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (table A).

A patient perspective could help either:

1. resolve any uncertainty that has been identified OR
1. provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **16 August 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with unresectable or metastatic melanoma

Table 1 About you, unresectable or metastatic melanoma, current treatments and equality

1. Your name	Jonathan Haines
2. Are you (please tick all that apply)	/☐ **A patient with unresectable or metastatic melanoma?** /☐ **A patient with experience of the treatment being evaluated?** ☐ A carer of a patient with unresectable or metastatic melanoma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Melanoma Focus
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) /☐ **Yes, my nominating organisation has provided a submission** ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ **I agree with it and will be completing**
5. How did you gather the information included in your statement? (please tick all that apply)	/☐ **I am drawing from personal experience**

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with unresectable or metastatic melanoma? **If you are a carer (for someone with unresectable or metastatic melanoma) please share your experience of caring for them**	The diagnosis took many months, though it was annoying rather than painful – a blood blister that wouldn't heal! I had an operation to remove half a big toe + some lymph nodes – painless with no measurable inconvenience – followed by a year's worth of immunotherapy. My non cancerous issues, such as an arthritic hip, an enlarged prostate, sleep apnoea and hay fever were instead the cause of pain and inconvenience, to the extent that I could largely ignore the cancer and its treatment.
7a. What do you think of the current treatments and care available for unresectable or metastatic melanoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	My immunotherapy has been very easy to cope with. Just a question of setting aside four weekly repeat sessions for scans and treatment. I can only recall a couple of days of constipation and one with diarrhoea about 4 months in (which both could have been dietary instigated) – so no side effects worth recording. Indeed, for all I know I could have just been receiving a saline solution each month! I have no knowledge of other's experience
8. If there are disadvantages for patients of current NHS treatments for unresectable or metastatic melanoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I found the whole process of receiving my treatment very straight forward – nothing to worry about – just sit back and relax! There are no disadvantages or side effects to record. I cannot comment about any other treatment as this is the only one I have experienced.
9a. If there are advantages of nivolumab–relatlimab over current treatments on the NHS please describe	As previously implied, the treatment itself had no impact on my quality of life – the issues I did have, and continue to have, were non cancerous.

these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nivolumab–relatlimab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	So, for me the treatment was totally non intrusive, which meant I could ignore it. I threw myself instead into fighting my non cancerous issues, firstly by committing myself to losing weight – some 10kg to date over the last 17months – and a low impact fitness regime averaging over 15,000 steps a day post op. All this, of course, could have helped my take up and processing of the treatment, but I hesitate to suggest that all patients should undertake the same regime!
10. If there are disadvantages of nivolumab–relatlimab over current treatments on the NHS please describe these. For example, are there any risks with nivolumab–relatlimab ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no experience of any other cancer treatment and certainly there are no disadvantages or side effects, so far, to that which I have received. I'm about to have my first set of 12 weekly scans post treatment so hopefully the results will remain positive. Certainly I don't feel anything untoward that might threaten my equilibrium.
11. Are there any groups of patients who might benefit more from nivolumab–relatlimab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	My experience should encourage anyone with a similar diagnosis to welcome the treatment whole heartedly – as far as I'm concerned, it's painless, non intrusive and has a high probability of generating zero/minimal side effects.
12. Are there any potential equality issues that should be taken into account when considering unresectable or metastatic melanoma and nivolumab–relatlimab ? Please explain if you think any groups of people with this condition are particularly disadvantaged	As per my answer just above – there are no equality issues relating to this treatment.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No – and thank you NHS for 'mending me'! I've met some lovely people and the care has been extraordinary.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma ID1688

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

NICE National Institute for Health and Care Excellence

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**Merck Sharp & Dohme (UK) Ltd**
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue1: Lack of clinical trial evidence for patients aged 12 to 18 years (EAG report 2.2.3, 2.3.2, 3.1 and 3.8)	No	We note that it is up to the MHRA, as the regulatory authority responsible for medicine marketing authorisation in the UK, to issue a decision on the risk:benefit profile of this technology in the proposed indication. NICE will then be expected to issue guidance per final GB MA.
Issue 2: Clinical effectiveness data are not available for patients for whom immune-oncology combination therapy is not suitable (EAG report 2.3.2, 3.7.1 and 3.8)	No	No further comment.
Issue 3: Both investigator-assessed and blinded independent central review (BICR)-assessed progression-free survival (PFS) data used in network meta-analyses (NMA; EAG report 3.4.1, 3.7.1, 3.7.3 and 3.8)	No	No further comment.

Issue 4: Uncertainties around fractional polynomial (FP) NMA model selection to estimate time-varying hazard ratios (HR; EAG report 3.7.3 and 3.8)	No	No further comment.
Issue 5: Difficulties interpreting PFS and overall survival (OS) FP NMA results (EAG report 3.7.3, 3.7.4 and 3.8)	No	No further comment.
Issue 6: Clinical effectiveness of nivolumab-relatlimab versus pembrolizumab: data limitations (EAG report 2.3.4, 3.7.1, 3.7.3 and 3.8)	No	We note that the manufacturer has used data from Robert et al 2019 "*Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study*. Lancet Oncol. 2019; 20:1239-51". As the results (with the exception of EAG analyses) are heavily redacted, we are not able to comment on their validity. However, a more recent publication by Robert et al 2023 ("*Seven-Year Follow-Up of the Phase III KEYNOTE-006 Study: Pembrolizumab Versus Ipilimumab in Advanced Melanoma*. J Clin Oncol. 2023 Jun 22:JCO2201599. doi: 10.1200/JCO.22.01599") reports the latest follow-up data from KEYNOTE-006. Therefore, these data should be incorporated in the evidence base and the impact of using this evidence should be explored.
Issue 7: Limited generalisability of company cost effectiveness results to NHS patients for whom immune-oncology combination therapy is not suitable (EAG report 6.1 and 6.11)	No	No further comment.
Issue 8: Uncertain RELATIVITY-047 trial long-term	No	No further comment.

OS data (EAG report 6.2, 6.3 and 6.11)		
Issue 9: Implausible proportions of patients reaching background mortality after progression (nivolumab-relatlimab versus nivolumab+ipilimumab and versus pembrolizumab; EAG report 6.2, 6.3 and 6.11)	No	No further comment.
Issue 10: Uncertain pembrolizumab NMA results: consequences for cost effectiveness results (EAG report 6.4.2 and 6.11)	No	See issue 6 response above pertaining to a later publication of KN-006.
Issue 11: A 2-year treatment stopping rule should not have been applied (EAG report 6.5)	No	It is up to the AC to determine which assumptions are appropriate given the trial design, available data, and clinical expert opinion.
Issue 12: Ipilimumab adverse event costs and disutilities applied after treatment with ipilimumab has stopped (EAG report 6.7)	No	No further comment
Issue 13: Company subsequent treatment assumptions (EAG report 6.6 and 6.11)	No	No further comment

Issue 14 Nivolumab-relatlimab has an EU marketing authorisation that limits use to patients with PD-L1 tumour expression <1% (EAG report 2.2.2, 2.3.2, 2.3.6, 2.3.7 and 3.8)	No	It is up to the MHRA, as the regulatory authority responsible for medicine marketing authorisation in the UK, to issue a decision on the risk:benefit profile of this medicine in the proposed indication. NICE will then be expected to issue guidance per final GB MA which may or may not require demonstration of cost-effectiveness by PD-L1 status if this is reflected in the GB MA issued.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Positioning within the current treatment pathway	Issue 1	No	The AC should consider the most appropriate positioning of nivolumab + relatlimab in the treatment pathway given the clinical effectiveness, safety profile and cost-effectiveness results.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma ID1688

Technical engagement response form

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If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Liverpool Reviews and Implementation Group (LRiG)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**NA**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**NA**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Lack of clinical trial evidence for patients aged 12 to 18 years (EAG report 2.2.3, 2.3.2, 3.1 and 3.8)	No	The company acknowledges that no clinical data are available to support the efficacy or safety of nivolumab-relatlimab in patients aged 12 to 18 years. Although rare, melanoma in adolescents behaves similarly to the disease in adults, and the treatment of adolescents and adults with immune checkpoint inhibitors, including nivolumab + relatlimab, is expected to have an equivalent risk-benefit profile to adults. Rationale for the extrapolating the benefit of adults to adolescents is outlined in the Opdualag EPAR[1], as also provided in the EAG clarification questions. *"No adolescents were included in the clinical studies. Given the similarity of disease histology, genetic background, treatment and prognosis of metastatic melanoma for adults and adolescents, and sufficiently comparable predicted drug exposure in adults and adolescents, based on popPK simulations in patients weighing at least 30 kg, extrapolation of efficacy and safety from adults to the adolescent population is considered acceptable. In these simulations, both the situation of a reduced clearance and volume of distribution of relatlimab and nivolumab, as well as the situation of a comparable clearance and volume of distribution in adolescents and adults, was simulated. In both cases the exposure is considered sufficiently comparable between adolescent and adult patients.*

		Therefore, inclusion of adolescents 12 years of age and older in the indication is considered approvable. *The available safety data of nivolumab in adolescents, indicate a comparable short term safety profile for adolescents as for adults. Given that nivolumab and relatlimab are both check-point inhibitors, also for relatlimab a comparable short term safety profile for adolescents and adults may be expected in case of comparable exposure. Long-term safety data are missing, especially the long-term effect of endocrine AEs might be different between adults and adolescents. Given the poor prognosis of adolescents with metastatic or unresectable (advanced melanoma), the uncertainty regarding the long-term toxicity profile is not considered a major concern. In addition, long-term safety will be followed - Assessment report EMA/720884/2022 Page 146/147 up post approval (cat 3 study).”* Although it is acknowledged there is no established NHS treatment pathway for patients aged 12 to 18 years with untreated unresectable or metastatic melanoma, the NICE guidelines for the assessment and management of melanoma (NG14) states that “the committee agreed that treatment should not differ between children and adults, and that recommendations also apply to children and young people”.[2]
EAG comment		If the NICE AC agrees that patients aged 12 to 18 years and patients aged ≥18 years have similar melanoma pathophysiology and treatment responses, then the clinical effectiveness evidence for patients aged ≥18 years can be used as a proxy for patients aged 12 to 18 years.
Issue 2: Clinical effectiveness data are not available for patients for whom immune-oncology combination therapy is not suitable (EAG report 2.3.2, 3.7.1 and 3.8)	No	The company disagrees with the language provided in this issue as the NICE guidelines for the assessment and management of melanoma (NG14)[2] do not use “IO combination” terminology to describe suitability. The company recognises that nivolumab + ipilimumab and nivolumab-relatlimab are combinations of IO therapies; however, while nivolumab may be in both treatment combinations, the mechanisms of action of ipilimumab and relatlimab are different and thus the therapies are not interchangeable. The company welcomes clinical expert opinion for consideration to address this issue.

		Regarding immunotherapies, NG14[2] part 1.8.8 states, “Offer nivolumab plus ipilimumab to people with untreated stage IV or unresectable stage III melanoma if suitable for them based on the factors in recommendation 1.8.6. [2022]” and section 1.8.9 states, “If nivolumab plus ipilimumab is unsuitable or unacceptable (for example, because of potential toxicity), offer pembrolizumab or nivolumab monotherapy. [2022]”. Section 1.8.6 of NG14 which determines suitability for nivolumab + ipilimumab, states “When choosing systemic anticancer treatment for untreated stage IV or unresectable stage III melanoma, base treatment decisions on the following factors: • comorbidities and performance status • risk of treatment toxicity • whether potential treatment toxicity will be tolerated • presence of symptomatic brain metastases • tumour biology (for example, high disease burden, rapid progression, lactate dehydrogenase level). Treatment decisions should be made after a full assessment of the risks and benefits by the treating oncologist and discussion with the person, in line with NICE's guideline on shared decision making.” Furthermore, recent consultation with clinicians has confirmed that the choice between the available IO treatments is individualised and ultimately based on its suitability for the patient. On consultation, UK clinicians expressed the opinion that nivolumab-relatlimab may also be a good alternative in patients either unfit to receive nivolumab + ipilimumab, or in centres without the capacity or experience to manage potential toxicities that arise from treatment with nivolumab + ipilimumab. Therefore, clinicians anticipated nivolumab-relatlimab to be used initially in patients who are currently receiving IO monotherapy.[3] The company appreciate that

		patients eligible for nivolumab-relatlimab may also be considered suitable for nivolumab + ipilimumab; however, many patients in NHS clinical practice are not suitable for nivolumab + ipilimumab and receive nivolumab or pembrolizumab monotherapy. However , as nivolumab-relatlimab has demonstrated similar clinical effectiveness to nivolumab + ipilimumab, but with a better safety profile, a comparison between nivolumab-relatlimab is also of relevance. The EAG report (2.3.2) states "It is unclear whether the available trial evidence (RELATIVITY-047 trial, CheckMate 067 trial and CheckMate 069 trial) should be used to inform decision-making for the population for whom nivolumab + ipilimumab is not suitable as these trials only recruited patients for whom IO combination therapy was considered suitable." The company wish to note that the suitability criteria for eligibility for nivolumab + ipilimumab per NG14 were developed after the CheckMate 067 trial. Therefore, patients who met the inclusion/exclusion criteria for RELATIVITY-047 were clinically suitable for nivolumab + ipilimumab, however given that the study started in 2018 and NICE approval for nivolumab + ipilimumab was in 2016, it is plausible that in practice patients would have not enrolled in RELATIVITY-047 and instead received nivolumab + ipilimumab. Of note, the patient populations enrolled into the RELATIVITY-047 and CheckMate-067 trials were highly similar. This is demonstrated through similarities in the eligibility criteria for trial enrolment, as presented in Table 1, and similar baseline demographics and disease characteristics of patients enrolled in RELATIVITY-047 and CheckMate-067, as demonstrated by the small standard mean difference values presented in Table 2. The baseline demographics and disease characteristics for the nivolumab arms of RELATIVITY-047 and CheckMate-067 are presented in the CS, Appendix D.4.2.4.2. Minimal differences were also seen between the nivolumab arms of the trials. In addition, it is noted that comparative clinical effectiveness for nivolumab-relatlimab versus nivolumab comes from the randomised, double-blind RELATIVITY-047 trial. There is no evidence to suggest that eligibility for nivolumab + ipilimumab would act as a treatment-effect modifier when estimating relative effectiveness.

Table 1: Key eligibility criteria for patients enrolled in RELATIVITY-047 and CheckMate-067

	RELATIVITY-047	CheckMate-067
Inclusion criteria	• Histologically confirmed Stage III (unresectable) or Stage IV melanoma, per the 8th edition of the AJCC staging system • No prior systemic anti-cancer therapy for unresectable or metastatic melanoma, but prior adjuvant or neoadjuvant melanoma therapy with a specified regimen was allowed (anti-PD-1, anti-CTLA-4, or BRAF-MEK containing regimen if ≥ 6 months between last dose and date of recurrence; interferon with last dose ≥ 6	• Histologically confirmed stage III (unresectable) or stage IV melanoma • No prior systemic treatment for advanced disease (i.e. no prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) • Males and females ≥ 18 years of age • ECOG performance status of 0 or 1 • Known BRAF V600 mutation status

			weeks before randomisation) • Males and females ≥ 12 years of age • ECOG performance status of 0 or 1, or a Lansky performance score ≥ 80% for minors • Known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the screening period		
		Exclusion criteria	• Active or untreated brain or leptomeningeal metastases • Uveal melanoma • Active autoimmune disease or condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14	• Active brain metastases or leptomeningeal metastases. Patients with brain metastases are eligible if these have been treated and there is no MRI evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first	

			days of start of study treatment • History of myocarditis	dose of study drug administration • Ocular melanoma • Patients with active, known or suspected autoimmune disease • Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration

Table 2: Baseline characteristics for patients in the nivolumab-relatlimab arm of RELATIVITY-047 and nivolumab + ipilimumab arm of CheckMate-067

	Nivolumab-relatlimab (n = 349)	Nivolumab + ipilimumab (n = 307)	SMD
Demographics			
Age (years)			[redacted]
Mean ± SD	61.22 ± 13.98	59.50 ± 13.63	
Sex, %			[redacted]
Male	205 (58.74)	201 (65.47)	
Female	144 (41.26)	106 (34.53)	
Race, %			[redacted]
White	336 (96.28)	303 (98.70)	
Non-White	7 (2.01)	4 (1.30)	
Missing / N	6 / 349 (1.72)	0 / 307 (0.00)	
Geographic region, %			[redacted]
Rest of World	312 (89.40)	246 (80.13)	
USA	37 (10.60)	61 (19.87)	
History of smoking, %			[redacted]
Never smoked	211 (60.46)	156 (50.81)	
Current/former	123 (35.24)	137 (44.63)	
Missing / N (%)	15 / 349 (4.30)	14 / 307 (4.56)	
Disease characteristics			

		Time from advanced melanoma diagnosis until randomization (years)			[redacted]	
		Mean ± SD	2.85 ± 4.85	3.57 ± 4.48		
		Prior adjuvant therapy, %			[redacted]	
		Not received	315 (90.26)	236 (76.87)		
		Received	34 (9.74)	71 (23.13)		
		AJCC M stage with LDH category 1, %			[redacted]	
		M0/M1any[0]	230 (65.90)	197 (64.17)		
		M1any[1]	119 (34.10)	110 (35.83)		
		AJCC disease stage, %			[redacted]	
		Stage III	35 (10.03)	16 (5.21)		
		Stage IV	314 (89.97)	291 (94.79)		
		Melanoma subtype, %			[redacted]	
		Cutaneous acral	39 (11.17)	11 (3.58)		
		Cutaneous non-acral	245 (70.20)	242 (78.83)		
		Mucosal	23 (6.59)	27 (8.79)		
		Other	42 (12.03)	27 (8.79)		
		History of brain metastases, %			[redacted]	
		No history of brain metastases	342 (97.99)	297 (96.74)		
		History of brain metastases	7 (2.01)	10 (3.26)		
		ECOG performance status, %			[redacted]	

		≥ 1	116 (33.24)	83 (27.04)	
		0	233 (66.76)	224 (72.96)	
		BRAF mutation status, %			[redacted]
		Mutation Wild type	216 (61.89)	206 (67.10)	
		Mutation positive	133 (38.11)	101 (32.90)	
		LDH category 1, %			[redacted]
		≤ ULN	223 (63.90)	194 (63.19)	
		> ULN	126 (36.10)	113 (36.81)	
		LDH category 2, %			[redacted]
		> 2 X ULN	31 (8.88)	36 (11.73)	
		≤ 2 X ULN	318 (91.12)	271 (88.27)	
		PD-L1 expression category, %			[redacted]
		< 1%/non-quantifiable	205 (58.74)	152 (49.51)	
		≥ 1%	144 (41.26)	155 (50.49)	

Furthermore, as an internal validation of the adjusted ITC between nivolumab-relatlimab and nivolumab + ipilimumab, the weighted nivolumab arms from both trials were compared for all safety and efficacy outcomes. An analysis using investigator-assessed PFS showed a similar hazard of progression or death for both nivolumab arms after weighting (HR [redacted], 95% CI: [redacted], [redacted]), with the point estimate of the HR close to 1 and the CI spanning 1. An analysis of OS showed a similar risk of mortality for both nivolumab arms after weighting (HR [redacted], 95% CI: [redacted], [redacted]), with the point estimate of the HR close to 1 and the CI spanning 1. This analysis therefore demonstrated that after weighting there were no differences in PFS and OS outcomes between the nivolumab arm of CheckMate-067 and the nivolumab arm of RELATIVITY-047.

<table>
<tr><td></td><td></td><td>These similarities collectively demonstrate that, although RELATIVITY-047 may plausibly provide evidence on patients who would not be treated with nivolumab + ipilimumab, the similarity of outcomes for patients treated with nivolumab in both trials, further supports their similarity.</td></tr>
<tr><td>EAG comment</td><td></td><td>In response to the factual accuracy check (FAC), the EAG amended the Issue 2 (and Issue 7) heading and summary text in the post-FAC EAR to improve clarity (as suggested by the company). The updated table is provided below for reference.

Issue 1 Lack of clinical effectiveness data for NHS patients who currently receive IO monotherapy
<table>
<tr><td>Report section</td><td>Error! Reference source not found., Error! Reference source not found. and Error! Reference source not found.</td></tr>
<tr><td>Description of issue and why the EAG has identified it as important</td><td>In NG14, it is recommended that NHS patients with untreated unresectable or metastatic melanoma:
for whom IO combination therapy (currently only nivolumab+ipilimumab) is suitable and acceptable, receive nivolumab+ipilimumab
for whom nivolumab+ipilimumab is not suitable or acceptable, receive pembrolizumab or nivolumab.
The EAG considers that all NHS patients treated with nivolumab+ipilimumab, and some patients treated with pembrolizumab or nivolumab, are patients for whom nivolumab-relatlimab would be suitable.

It is unclear whether the available trial evidence should be used to inform decision-making for the population for whom nivolumab+ipilimumab is not suitable or acceptable as the RELATIVITY-047 trial, CheckMate 067 trial and CheckMate 069 trial only recruited patients for whom IO combination therapy (nivolumab-relatlimab or nivolumab+ipilimumab) was considered suitable and acceptable.</td></tr>
<tr><td>What alternative</td><td>None</td></tr>
</table></td></tr>
</table>

		approach has the EAG suggested? |
		What is the expected effect on the cost effectiveness estimates? | Unknown
		What additional evidence or analyses might help to resolve this key issue? | Seek clinical opinion.
		EAG=External Assessment Group; IO=immuno-oncology; NG=NICE Guidance The EAG considers that, since the RELATIVITY-047 trial only recruited patients for whom immuno-oncology (IO) combination therapy (i.e., nivolumab+ipilimumab or nivolumab-relatlimab) was suitable and acceptable and, that the RELATIVITY-047 trial does not provide evidence for patients for whom IO combination therapy is not suitable or acceptable and who would receive IO monotherapy (i.e., pembrolizumab or nivolumab) in NHS clinical practice.
Issue 3: Both investigator-assessed and blinded independent central review (BICR)-assessed progression-free survival (PFS) data used in network meta-analyses (NMA; EAG report 3.4.1, 3.7.1, 3.7.3 and 3.8)	No	Of the two measures for assessing disease progression, the company retains that BICR is the preferred measure. This is for the reasons outlined in the response to clarifications and briefly summarised below: • The assessment of nivolumab-relatlimab should utilise PFS per BICR to inform estimates as this is the primary study endpoint in RELATIVITY-047 for which the trial was appropriately powered. PFS per investigator-assessment was an exploratory endpoint for which RELATIVITY-047 was not powered to demonstrate differences by treatment • PFS per BICR is referred to as the gold standard for disease progression as it is more objective than PFS per investigator-assessment.[4] This view is well advocated by EMA and FDA guidance[5, 6] • BICR is favoured as it removes assessment bias between readers, reduces variability and increases accuracy in determining if a patient has progressed, thus counteracting many issues that can often arise from investigator-

		assessment a point acknowledged by the EAG in their report; Section 3.4.1 "The EAG agrees with the company that the use of BICR for the objective assessment of radiological outcomes can reduce the risk of systematic investigator bias which may favour one treatment arm"
EAG comment		The EAG emphasises that the issue relates to the use of a mixture of BICR-assessed and investigator-assessed PFS in the NMAs and not to the relative advantages of BICR assessment compared to investigator assessment of outcomes. Investigator-assessed PFS data were available from all four trials therefore the EAG conducted a constant HR NMA using investigator-assessed PFS data.
Issue 4: Uncertainties around fractional polynomial (FP) NMA model selection to estimate time-varying hazard ratios (HR; EAG report 3.7.3 and 3.8)	No	The company agrees with the EAG that clinical plausibility is very important when choosing a statistical model. This is why the clinical plausibility of the four best-fitting models (based on deviance information criterion [DIC]) was used to inform the choice of model (CS B.3.3.2 and response to EAG CQ A10). All extrapolations of time-to-event data in the model were performed and selected following statistical best-practice as outlined in the NICE TSDs 14 and 21.[7, 8] Models were therefore selected based on: - Assessment of proportional hazards - Visual fit to the observed KM data within trial periods - Assessment of the underlying hazard functions - Statistical goodness of fit (based on AIC, BIC or DIC as appropriate) - Validation by clinicians with experience of treating unresectable or metastatic melanoma It is further noted that clinical plausibility relates to both good within-sample fit and plausible extrapolations. Model fit statistics (such as the DIC) provide information on the former and so form an important part of assessing clinical plausibility; models with poor within-sample fit are unlikely to be clinically plausible.

EAG comment		The EAG acknowledges that the company assessed clinical plausibility but retains that the company only conducted clinical plausibility assessments of the two FP models for PFS and the four FP models for OS with the lowest DIC statistics out of a possible 22 FP OS and PFS models (CS, Appendix D, Table 13 and Table 14, response to clarification question A10). The EAG emphasises that **all** FP models which provide clinically plausible results should be considered **before** model fit statistics are considered. The EAG notes that the DIC statistic is a measure used to compare model fit to aid model selection (i.e., the model with the lowest DIC can be considered to provide the best fit of the models under consideration to the available data). However, the DIC statistic itself does not provide any information about whether the within-sample fit of the model is adequate; the residual deviance and the effective number of model parameters are the measures required to assess the within-sample fit of a model (Dias 2018). The EAG also emphasises that FP models which have a similar level of fit according to DIC statistics may generate very different long-term survival estimates. The two PFS FP models and the four OS FP models with the lowest DIC statistics, only one model for each outcome was deemed to provide clinically plausible results, despite there being less than 3 points difference in their DIC statistics. The EAG maintains that the DIC statistic is not a measure of clinical plausibility and should only be used in model selection once clinical plausibility has been established.
Issue 5: Difficulties interpreting PFS and overall survival (OS) FP NMA results (EAG report 3.7.3, 3.7.4 and 3.8)	No	In their report the EAG states that it "…considers that it is not appropriate to infer statistical significance (or lack of) from the FP NMAs 95% CrIs" The company notes that deterministic estimates of cost-effectiveness are based on point estimates, whilst probabilistic estimates of cost-effectiveness (including estimates of uncertainty) are derived via Monte Carlo sampling. As such, inferences around statistical significance will not impact on decision-making.

		The company acknowledges that there are strengths and limitations with each of the approaches to performing indirect comparisons (FP NMA, constant HR NMA, adjusted ITC). The company acknowledges that the EAG approach to estimating OS and PFS may also be used for decision-making: • nivolumab-relatlimab versus nivolumab: RELATIVITY-047 trial • nivolumab-relatlimab versus nivolumab + ipilimumab: adjusted ITCs • nivolumab-relatlimab versus pembrolizumab: EAG constant HR NMAs
EAG comment		The EAG considers that it is not appropriate to infer statistical significance (or lack of) from the FP NMA 95% CrIs because time varying HRs reflect the amount of data overall and not the number of patients providing data at each time point. The EAG considers that the best available clinical effectiveness evidence for comparisons between treatments for PFS and OS are: • nivolumab-relatlimab versus nivolumab: RELATIVITY-047 trial (**suitable for decision making**; used in an EAG model scenario) • nivolumab-relatlimab versus nivolumab+ipilimumab: adjusted ITCs (**suitable for decision making**; used in an EAG model scenario) • nivolumab-relatlimab versus pembrolizumab: EAG constant HR NMAs (**not suitable for decision making**; not used in an EAG model scenario).
Issue 6: Clinical effectiveness of nivolumab-relatlimab versus pembrolizumab: data limitations (EAG report 2.3.4, 3.7.1, 3.7.3 and 3.8)	No	The company notes that decision-making should make best use of the available evidence. For the indirect comparison of nivolumab-relatlimab versus pembrolizumab there is evidence on effectiveness outcomes over time from two large, well-conducted trials: RELATIVITY-047 and KEYNOTE-006.
EAG comment		For the comparison of nivolumab-relatlimab versus pembrolizumab, despite violation of the proportional hazards (PH) assumption in the PFS and OS constant HR NMAs, the EAG considers that the best available clinical effectiveness results are generated by the EAG constant HR NMAs (rather than the company FP NMA

		results). However, the EAG considers that the EAG constant HR NMA results are **not suitable for decision making** and should not be used to generate cost effectiveness results for the comparison of nivolumab-relatlimab versus pembrolizumab. Clinical advice to the EAG was that the clinical effectiveness and safety profiles of pembrolizumab and nivolumab are very similar. The EAG therefore ran an alternative scenario analysis in which the PFS/OS for pembrolizumab was set equal to the PFS/OS for nivolumab (RELATIVITY-047 trial data) to inform decision making.
Issue 7: Limited generalisability of company cost effectiveness results to NHS patients for whom immune-oncology combination therapy is not suitable (EAG report 6.1 and 6.11)	No	The company reiterate that NG14 refers to "nivolumab + ipilimumab" suitability and not as "IO combination". The relevance of clinical effectiveness data to NHS patients for whom nivolumab + ipilimumab is not suitable is described in detail in issue 2. Key points pertinent to the cost-effectiveness results are summarised here. • The company recognises that nivolumab + ipilimumab and nivolumab-relatlimab are combinations of IO therapies; however, the therapies are not interchangeable. • If patients who met the inclusion/exclusion criteria for RELATIVITY-047 were clinically suitable for nivolumab + ipilimumab, it is plausible that they would have not enrolled in RELATIVITY-047 and instead received nivolumab + ipilimumab. The company welcomes clinical expert opinion for consideration to address this issue. • Consultation with clinicians has confirmed that the choice between the available IO treatments is individualised and ultimately based on suitability of the patient. Nivolumab-relatlimab may be used initially in patients who are currently receiving IO monotherapy.
EAG comment		The RELATIVITY-047 trial (eligible for treatment with nivolumab-relatlimab) and CheckMate 067 (eligible for treatment with nivolumab+ipilimumab) and CheckMate 069 trial (eligible for treatment with nivolumab+ipilimumab) populations were similar; however, these patients are no longer likely to be representative of patients who receive IO monotherapy in NHS clinical practice. Therefore, it is unclear

		whether cost effectiveness results generated by the company model are generalisable to NHS patients. See EAG response to Issue 2.
Issue 8: Uncertain RELATIVITY-047 trial long-term OS data (EAG report 6.2, 6.3 and 6.11)	No	The company acknowledges that there is uncertainty regarding long-term OS extrapolations for nivolumab-relatlimab used in the cost-effectiveness model. However, the OS data from RELATIVITY-047 provided in this submission is the best available evidence for nivolumab-relatlimab in this indication. The EAG noted that they were not able to provide more reliable OS extrapolations based on the latest data cut from RELATIVITY-047 (EAG Report 6.3.2). The company also notes that the three evidence sources deemed by the EAG to be the best available for estimating OS (listed in Issue 5) each demonstrates an OS benefit for nivolumab-relatlimab (against nivolumab, nivolumab + ipilimumab and pembrolizumab). The company accepts that there is uncertainty around the long-term OS hazards, however extrapolations were chosen based on NICE DSU TSD 14 and 21 guidance, including validation by clinicians with experience of treating advanced melanoma patients in England (CS B.3.3.2). Clinicians advised that, given that nivolumab-relatlimab features nivolumab in combination, there was no reason to think it would not demonstrate similar long-term survival profiles to the other IOs. The NMA performed by the company resulted in a constant HR against nivolumab + ipilimumab of [redacted] (95% confidence interval [redacted], [redacted]) indicating an OS advantage for nivolumab-relatlimab. Time-varying HRs from the same NMA showed nivolumab-relatlimab was associated with a numerical advantage in OS in comparison with nivolumab + ipilimumab at month 3 ([redacted] [redacted], [redacted]) to month 12 ([redacted] [redacted], [redacted]), performed similarly at month 18 (1 [redacted], [redacted]) and was associated with a slight numerical disadvantage from month 24 ([redacted] [redacted], [redacted]) to month 48 ([redacted] [redacted], [redacted]). The OS HR after weighting from the company's adjusted ITC is [redacted] ([redacted], [redacted]), again indicating a slight advantage for nivolumab-relatlimab.

<table>
<tr><td></td><td></td><td>We do not believe any further analyses can be provided to improve the existing approach, therefore the company maintains its preferred approach to modelling OS used in the company base-case.</td></tr>
<tr><td>EAG comment</td><td></td><td>No additional comment.</td></tr>
<tr><td>Issue 9: Implausible proportions of patients reaching background mortality after progression (nivolumab-relatlimab versus nivolumab + ipilimumab and versus pembrolizumab; EAG report 6.2, 6.3 and 6.11)</td><td>Yes</td><td>The company believes that when considering estimates of post-progression survival, it is more informative to consider estimates taken from the same time-point.

Observed data for immunotherapies in this indication (nivolumab, nivolumab + ipilimumab, ipilimumab in CheckMate-067; pembrolizumab, ipilimumab in KEYNOTE -006) show that there are still divergences in observed long-term PFS and OS indicating that there may be up to 15% of patients alive after disease progression at 84 to 90 months (Table 3 and Table 4).
Table 3: 90-month survival outcomes CheckMate-067

<table>
<tr><th>Treatment arm</th><th>PFS at 90 months</th><th>OS at 90 months</th></tr>
<tr><td>Nivolumab + ipilimumab</td><td>48%</td><td>33%</td></tr>
<tr><td>Nivolumab</td><td>42%</td><td>27%</td></tr>
<tr><td>Ipilimumab</td><td>22%</td><td>7%</td></tr>
<tr><td colspan="3">Adapted from Figure 2 of Hodi et al. 2022.[9]</td></tr>
</table>
Table 4: 84-month survival outcomes from KEYNOTE -006

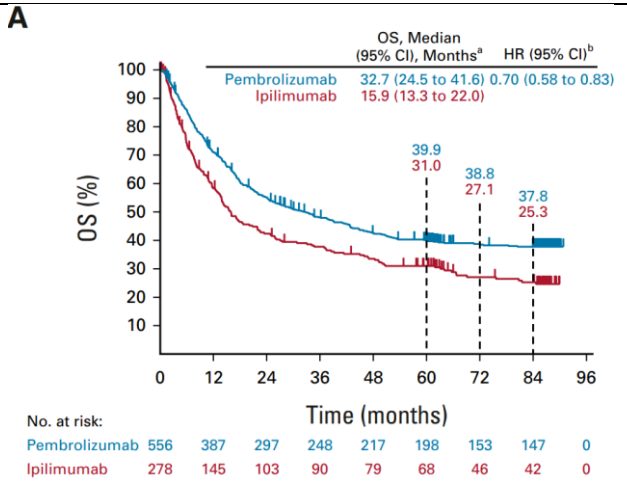
<table>
<tr><th>Treatment arm</th><th>mPFS at 84 months</th><th>OS at 84 months</th></tr>
<tr><td>Pembrolizumab</td><td>26.8%</td><td>41.2%</td></tr>
<tr><td>Ipilimumab</td><td>15.9%</td><td>27.6%</td></tr>
<tr><td colspan="3">Adapted from Figure A2 of Robert et al, 2023.[10]</td></tr>
</table>
</td></tr>
</table>

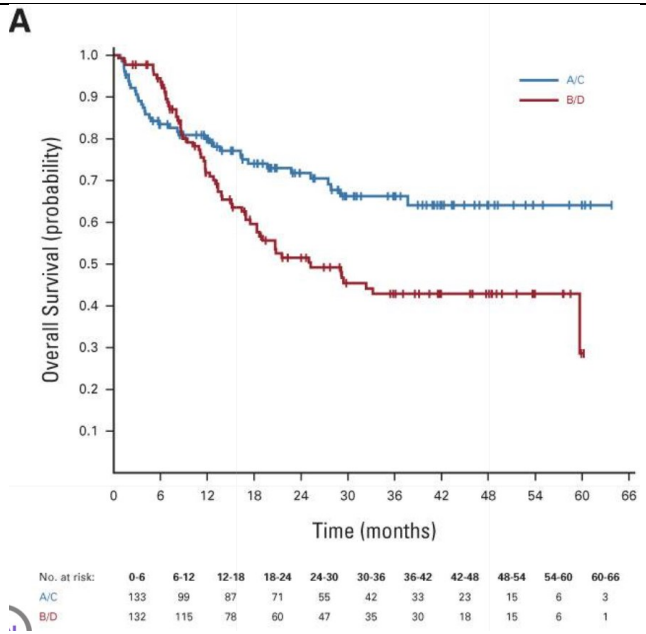
		Furthermore, as noted in the original submission, the company approach to modelling PFS is likely to underestimate long-term PFS for nivolumab-relatlimab as it fails to capture the plateau observed in the KM data. This leads to inflated estimates of the number of patients remaining in the progressed disease state. The observed differences in long-term OS and PFS (and hence also post-progression survival) between the two combination treatments (nivolumab-relatlimab and nivolumab-ipilimumab) are consistent with results of the adjusted indirect comparison, which demonstrate (based on point estimates) a slight increase in OS for nivolumab-relatlimab coupled with a slight decrease in PFS.
EAG comment		When estimating PPS, the company considers that it is useful to assess PFS and OS K-M data at the same time point. The EAG considers that this approach is appropriate for estimating model health state occupancy. However, the EAG considers that when determining the shape of the PPS curve over time, data from the same time point are not helpful as PFS and OS K-M data are measured from time zero, whereas PPS K-M data are measured from the time each individual patient progresses. The EAG has presented estimates of different proportions of patients in the PFS, PPS and OS health states who are 'cured' to allow assessment of the comparative plausibility of long-term survival occurring before or after progression at different rates for different treatments.
Issue 10: Uncertain pembrolizumab NMA results: consequences for cost effectiveness results (EAG report 6.4.2 and 6.11)	No	For both OS and PFS indirect comparisons using both time-varying and fixed hazard ratios were performed. For PFS the EAG also performed an additional fixed hazard ratio analysis using IA PFS. These analyses all collectively demonstrated superior outcomes for nivolumab-relatlimab versus pembrolizumab for both OS and PFS. Indirect comparisons also demonstrate that pembrolizumab provides inferior OS and PFS to nivolumab (EAG report, Table 20). As such, the company believes that

		the KEYNOTE-006 trial provides the best available evidence to inform the effectiveness of pembrolizumab.
EAG comment		The EAG maintains that due to the violation of PH in some of the data used to generate EAG constant HR NMA results (nivolumab-relatlimab versus pembrolizumab), results from this NMA should not be used in the cost effectiveness model.

Issue 11: A 2-year treatment stopping rule should not have been applied (EAG report 6.5)	Yes	The decision to include a 2-year stopping rule for all immunotherapies was based on clinical advice to the company, previous NICE appraisals in this indication and the NICE melanoma HEMR. The company would like to re-iterate that natural waning to general population mortality hazards is applied in the cost-effectiveness model (CS B.3.3.3, B.3.3.6). This is supported by long-term data from the CheckMate-067 trial which shows nivolumab + ipilimumab OS hazards reaching general population mortality at approximately 5 years[11], within the trial follow-up. As this natural waning effect is observed, there is no need to implement further exploratory waning in the model. Furthermore, clinical experts noted that for all treatment arms in the model if patients have not died or progressed at 3-5 years they would be unlikely to progress or die from melanoma[3]. As nivolumab-relatlimab includes nivolumab, clinical expert position was that any long-term outcomes would be similar to that observed for IOs; i.e. with a long-term plateau in survival. Of note, natural waning occurs for nivolumab-relatlimab before it occurs for any of the other treatments. Hence the treatment effect of nivolumab-relatlimab is waned more than the treatment effects of the other IOs. Clinical advice to the EAG (EAG report 6.5.2) was that treatment is usually discontinued at or before two years due to toxicity associated with immunotherapy treatment. Further clinical advice sought by the company during technical engagement confirmed this, consistently noting that stopping treatment at two years was extremely common, and in-line with Blueteq Approval Criteria.[12] The company welcomes further clinical expert opinion for consideration to address this issue. Whilst no stopping rules were specified in NICE recommendations for nivolumab, pembrolizumab and nivolumab + ipilimumab in this indication, it is unusual for stopping rules to be specified in NICE recommendations. For example, TA817, TA818, TA857 and TA865 included stopping rules in their pivotal trials but these were not specified in their respective recommendations. Due to their mechanisms

		of action, the clinical effect of IO therapies extends beyond a patient completing their treatment, providing long-term survivorship in a subset of patients. The company would like to re-iterate the existence of data, both from CheckMate-067[13], and real-world evidence[14] which demonstrate favourable long-term outcomes amongst patients who discontinued treatment with an immunotherapy prior to two years. This data was supported by UK clinicians based on their experience of using IO treatments in melanoma[3]. In addition, since the original company submission, seven-year follow-up from KEYNOTE-006 has been published[10]. In this study pembrolizumab was given for a maximum of two years, whilst ipilimumab was given for up to 12 weeks. Results, for both the overall and treatment naïve population, demonstrate both a persistent plateau in survival, and a persistent treatment effect for pembrolizumab (Figure 1). These findings are further supported by pooled long-term findings from ipilimumab monotherapy studies: data from almost 2,000 patients with follow-up to ten years demonstrates a sustained plateau in OS. **Figure 1: Kaplan-Meier estimates of OS by randomized treatment in the overall Keynote-006 population[10]**

		A  Further, the DREAMseq trial (which compared nivolumab + ipilimumab with combination targeted therapy in treatment-naïve patients with unresectable advanced BRAF-mutant melanoma) included a maximum treatment duration for nivolumab + ipilimumab of 84 weeks[15]. Three-year overall survival for nivolumab + ipilimumab was 66.2%, with a clear plateau out to five years (this compares with a three-year overall of 58% for nivolumab + ipilimumab in CheckMate 067) (Figure 2). **Figure 2: Kaplan-Meier curve of OS for treatment sequences in DREAMseq[16]**

		 **Key:** A/C, patients receiving nivolumab + ipilimumab followed by dabrafenib + trametinib, B/D, patients receiving dabrafenib + trametinib followed by nivolumab + ipilimumab As noted in the company submission, the concept of long-term survivorship for IO melanoma treatments was consistently supported by UK clinicians, who saw no biological rationale for nivolumab-relatlimab acting differently given that nivolumab-relatlimab features nivolumab in combination . The company therefore considers that a two-year stopping rule for the modelled treatments is consistent with UK clinical practice and all previous PD-L1 targeted treatment in melanoma, whilst appropriately accounting for the cost of all these treatments to the NHS. Further, the use of a two-year stopping rule does not impact on the long-term effectiveness of immunotherapy treatment in advanced melanoma.

EAG comment		The EAG agrees with the company that long-term survival may still be expected for patients who discontinue treatment at or prior to 2 years. However, the EAG re-iterates that a substantial proportion of patients remained on treatment after 2 years in the RELATIVITY-047 and CheckMate-067 trials. These patients were likely to be receiving clinical benefit from treatment (as described by the clinician in the company response to consultation). The survival outcomes for these patients (and the extent to which survival differs across treatments), had they discontinued treatment at or prior to 2 years, are unknown. The EAG also notes that the incremental QALYs between comparators (in both the company and EAG analyses) are small and slight changes to survival outcomes (QALYs) are likely to have a large impact on cost effectiveness results. The EAG therefore considers it more appropriate to remove the stopping rules so that modelled outcomes are consistent with the treatment duration observed in the RELATIVITY-047 and CheckMate-067 trials.
Issue 12: Ipilimumab adverse event costs and disutilities applied after treatment with ipilimumab has stopped (EAG report 6.7)	Yes	The company agrees with the EAG that rates of adverse events may not be constant over-time, particularly for nivolumab + ipilimumab. However, it is noted that for nivolumab + ipilimumab the EAG approach uses average rates of adverse events (derived from the full trial follow-up) during the combination phase, followed by rates for nivolumab during the monotherapy phase. The company disagrees with the EAG's proposed approach as it is unlikely to reflect how rates of adverse events for nivolumab + ipilimumab change over time. Patients who receive nivolumab + ipilimumab and experience a TRAE during the combination phase may experience this due to nivolumab, due to ipilimumab, or due to the combination. The median onset of TRAEs in patients who receive nivolumab monotherapy and experience a TRAE is between 5 weeks (skin-related TRAEs) and 15 weeks (renal TRAEs).[17] Therefore, using the rates of AEs to inform disutility associated with nivolumab monotherapy (including the first three months of treatment) but applying this to the nivolumab + ipilimumab arm is likely to overestimate the adverse event disutility in the nivolumab + ipilimumab arm in favour of nivolumab-relatlimab. The

		company recognizes that the company base case may also have overestimated disutility due to AEs by assuming a constant rate. An alternative approach is to implement a one-off impact of adverse events on costs and utilities. For consistency, this approach is implemented for all treatments. This approach slightly reduces the ICER to nivolumab from [redacted] in the company base case to [redacted]. Nivolumab-relatlimab dominates nivolumab + ipilimumab and pembrolizumab in both approaches. In support of the one-off approach, it is noted that when comparing rates of adverse events between CheckMate 067 data cuts ('minimum 5-years follow-up'[13] and 'minimum 6.5-years follow-up'[18]) there were no additional treatment-related adverse events of any grade for either nivolumab + ipilimumab or ipilimumab, and only one additional adverse event for nivolumab.
EAG comment		The EAG considers that the company's alternative approach of modelling a one-off impact of AEs on costs and utilities is reasonable.
Issue 13: Company subsequent treatment assumptions (EAG report 6.6 and 6.11)	Yes/No	The company's approach to modelling subsequent treatments was based on the approach employed in the NICE melanoma HEMR. In the company's base case the proportion of patients receiving subsequent treatment after discontinuing each treatment arm was taken from the NICE melanoma HEMR. The distribution of subsequent therapies combined the treatment rules cited in the NICE HEMR and the proportion of patients with BRAF mutant or BRAF wild-type cancer in RELATIVITY-047. When estimating the proportion of patients that receive subsequent therapy, the company agree with the EAG that rates of subsequent systemic therapy are more informative than overall rates of subsequent treatment. However, the company does not agree with the EAG that rates of subsequent treatment would be the

		same between nivolumab-relatlimab and nivolumab, nor does it agree that the proportion of subsequent treatments would be the same for the two treatments. Amongst the patients who received subsequent systemic treatment in RELATIVITY-047, the proportion who received ipilimumab second-line (either as monotherapy or in combination with nivolumab) was [redacted]% ([redacted] / [redacted]) for first-line nivolumab-relatlimab and [redacted]% ([redacted] / [redacted]) for nivolumab, a relative increase of 52%. This demonstrates that nivolumab-relatlimab and nivolumab cannot be assumed to result in the same distribution of subsequent treatments, particularly as with longer follow-up from RELATIVITY 047 the proportion of patients in the nivolumab arm who subsequently receive ipilimumab second line is expected to further increase. Based on clinical feedback to the company, rates of treatment-related toxicity first line will influence both the proportion of patients who receive subsequent systemic treatment along and the distribution of subsequent treatments offered (in particular, notable toxicity first line meant that use of ipilimumab second-line was unlikely). As noted in the company submission, in RELATIVITY-047 a larger proportion of patients discontinued therapy due to a TRAE (Grade 3+) in the nivolumab-relatlimab arm versus the nivolumab arm (increase of [redacted]%). Hence, given that 48% of patients receiving nivolumab first-line received a subsequent systemic treatment in CheckMate 067, the rate would be [redacted]% for nivolumab-relatlimab. Consultation with clinicians confirmed that, following first-line treatment with nivolumab-relatlimab, BRAF mutant patients would likely receive a targeted treatment second-line. This is aligned with the company and EAG approach for BRAF mutant patients, and the NICE melanoma HEMR. There was more variability in the approach taken for BRAF wild-type patients. Use of ipilimumab second-line would be influenced by the availability of clinical trials, with an estimated 20% to 40% of BRAF wild-type patients receiving ipilimumab, and the remainder undertaking a clinical trial. Given this uncertainty, for modelling

purposes it is assumed that the high-point (40%) of BRAF wild-type patients who receive a second-line treatment receive ipilimumab.

In the original submission, it was assumed, in accordance with the NICE melanoma HEMR, that the mean time on second-line treatment would be 8.81 and 7.77 months with 0% and 61.5% second-line ipilimumab use, respectively (actual duration of treatment was not linked to the individual treatments received). As the revised approach for nivolumab-relatlimab is approximately half-way between the original approaches, a mean duration of 8.29 months is used.

To summarise, this results in the following approach to modelling subsequent therapies:

Treatment	**Patients receiving subsequent therapy (%)**
Nivolumab-relatlimab	[redacted]%
Nivolumab	48.00%
Nivolumab + ipilimumab	35.00%
Pembrolizumab	48.00%

Subsequent treatment	**Distribution receiving each subsequent therapy after nivolumab-relatlimab**	**Justification**
Dabrafenib + trametinib	19.26%	38.52% (equally split between dabrafenib + trametinib and encorafenib +
Encorafenib + binimetinib	19.26%	

		binimetinib) corresponding to the proportion of BRAF-mutant patients in RELATIVITY-047
Chemotherapy (dacarbazine) or clinical trials	36.89%	60% of the BRAF wild-type patients in RELATIVITY-047
Ipilimumab	24.59%	40% of the BRAF wild-type patients in RELATIVITY-047

This results in an increase in the ICER of nivolumab-relatlimab to nivolumab from the company base case at [redacted] to [redacted]. Nivolumab-relatlimab dominates nivolumab + ipilimumab and pembrolizumab in both approaches. |
| EAG comment | | The EAG agrees with the company that the proportion of patients receiving subsequent systemic treatment and the proportion of these patients receiving ipilimumab in the second-line setting are largely determined by the toxicity of first-line treatments. The company has assumed that it is reasonable to use the mid-point between the proportions of RELATIVITY-047 trial patients in the nivolumab-relatlimab arm and in the nivolumab arm receiving subsequent treatments. The EAG highlights that, in the RELATIVITY-047 trial, a higher proportion of patients discontinued treatment due to a TRAE (Grade 3+) in the nivolumab-relatlimab arm compared to patients in the nivolumab arm. This difference is smaller than the difference in the TRAE (any grade) discontinuation rate (adjusted ITC) between patients treated with nivolumab-relatlimab and patients treated with nivolumab+ipilimumab (CS, Table 23).

The EAG acknowledges that there is uncertainty around the proportion of patients that receive subsequent systemic therapy and the proportion of these patients who |

		receive ipilimumab in the second-line setting following treatment with nivolumab-relatlimab in the first-line setting but considers that both proportions may be higher than the values suggested by the company. The subsequent treatment costs for patients who were treated with nivolumab-relatlimab in the first-line setting may therefore be underestimated and cost effectiveness results may be optimistic and favour treatment with nivolumab-relatlimab. The EAG has included the proportion of (BRAF wild-type) patients receiving either ipilimumab (40%) or clinical trial treatments (60%) in the second-line setting in the EAG probabilistic sensitivity analysis to ensure probabilistic results account for that uncertainty. Further clinical advice about the proportions of NHS patients receiving different systemic treatments in the second-line setting would be informative.
Issue 14 Nivolumab-relatlimab has an EU marketing authorisation that limits use to patients with PD-L1 tumour expression <1% (EAG report 2.2.2, 2.3.2, 2.3.6, 2.3.7 and 3.8)	No	The MHRA appraisal of nivolumab-relatlimab is currently ongoing, with the decision anticipated in [redacted]. The anticipated indication under appraisal, as per the draft MHRA label, states: [redacted][19] As the CS aligns to the anticipated indication, which also aligns to that of the RELATIVITY-047 trial, no further analyses are required at this stage.
EAG comment		No additional comment.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

The EAG has been able to reproduce all the company cost effectiveness results (Table 4 and Table 5). Company base case and EAG alternative scenario cost effectiveness results generated using confidential prices are presented in the EAG post-technical engagement confidential appendix.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Company base case following EAG clarification questions (including corrections to HCRU costs and severity modifier)	-		ICER to nivolumab: [redacted] (all stated ICERs are per QALY) ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates ICER to pembrolizumab: nivolumab-relatlimab dominates
Key issue 3: Both investigator-assessed and BICR-assessed PFS data used in NMAs Key issue 5: Difficulties interpreting PFS and OS FP NMA results	Comparison versus nivolumab: PFS based on BICR, uses separate piecewise models: KM (first 3 months) + Gompertz. Comparison vs nivolumab + ipilimumab using FP NMAs for	Comparison versus nivolumab: PFS based on IA, uses separate piecewise models: KM (first 3 months) + Gompertz. Comparison vs nivolumab + ipilimumab: use of adjusted	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)

	both OS and PFS (using both BICR and IA) Comparison vs pembrolizumab using FP NMAs for both OS and PFS (using both BICR and IA)	indirect comparison for OS and PFS by IA. Comparison vs pembrolizumab: Constant HRs taken from NMA for OS and PFS by IA	
Key issue 12: Inappropriate AE costs and disutilities applied for patients treated with nivolumab + ipilimumab	AE costs and disutilities applied on a per-cycle basis.	AE costs and disutilities applied as a one-off in the first cycle	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)
Key issue 13: Company subsequent treatment assumptions	The proportion of patients going on to receive subsequent therapies based on rates of subsequent treatment from CheckMate-067 for nivolumab and nivolumab + ipilimumab. Nivolumab-relatlimab assumed to be [redacted]% lower than nivolumab reflecting the difference in treatment discontinuations due to a TRAE (Grade 3+) in the RELATIVITY-047 trial. The distribution of patients to each subsequent therapy was based on the proportion of BRAF-mutant patients in RELATIVITY-047 and treatment	The proportion of patients going on to receive subsequent therapies based on subsequent systemic therapies in CheckMate-067 for nivolumab and nivolumab + ipilimumab. Nivolumab-relatlimab assumed to be [redacted]% lower than nivolumab reflecting the difference in treatment discontinuations due to a TRAE (Grade 3+) in the RELATIVITY-047 trial. Based on clinical expert opinion, the distribution of subsequent treatments following fist-line nivolumab-relatlimab was assumed to be: targeted	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)

	rules used in the NICE melanoma HEMR. Pembrolizumab assumed equal to nivolumab for both rates of and distribution of subsequent treatments.	treatment for BRAF mutant patients (no change from before), ipilimumab for 40% of BRAF wild-type patients and clinical trials / chemotherapy for the remaining 60% Pembrolizumab assumed equal to nivolumab for both rates of and distribution of subsequent treatments.	
Treatment beyond progression (EAR 6.5.1)	Treatment duration capped at disease progression for all treatments.	Removed cap on treatment duration at progression.	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)
EAG revision to company IV administration costs (EAR 6.9)	SB14Z (weighted average of settings) for the first administrations of nivolumab-relatlimab, nivolumab, and pembrolizumab, and for the first four doses of nivolumab + ipilimumab. - £526.52 SB15Z (weighted average of settings) for all subsequent administrations. - £470.62	EAG's preferred input costs used. SB12Z (outpatient) for all doses of nivolumab-relatlimab, nivolumab, and pembrolizumab. - £281.11 SB14Z (outpatient) cost to estimate the administration cost of the first four doses of nivolumab + ipilimumab. - £342.66	ICER to nivolumab: [redacted] ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: nivolumab-relatlimab dominates (no change)
Company's base case following technical engagement (or revised	Incremental QALYs against nivolumab: [redacted]	Incremental costs against nivolumab: [redacted]	ICER to nivolumab: [redacted]

base case). Including the EAG preferred approach to modelling PFS for nivolumab-relatlimab and nivolumab; AEs applied as a one-off; subsequent treatment proportions and distributions for nivolumab-relatlimab modelled as halfway between nivolumab + ipilimumab and nivolumab; treatment beyond progression and changes to IV administration costs.	Incremental QALYs against nivolumab + ipilimumab: [redacted] Incremental QALYs against pembrolizumab: [redacted]	Incremental costs against nivolumab + ipilimumab: [redacted] Incremental costs against pembrolizumab: [redacted]	ICER to nivolumab + ipilimumab: nivolumab-relatlimab dominates (no change) ICER to pembrolizumab: Nivolumab-relatlimab dominates (no change)

Sensitivity analyses around revised base case

Table 5: Fully incremental probabilistic analysis of company's revised base case (1,000 iterations)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental ICER
Nivolumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,695
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	-	-	-	Strictly Dominated
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	Strictly Dominated

Figure 3: Cost-effectiveness plane of company's revised base case

Figure 4: Cost-effectiveness acceptability curve of company's revised base case

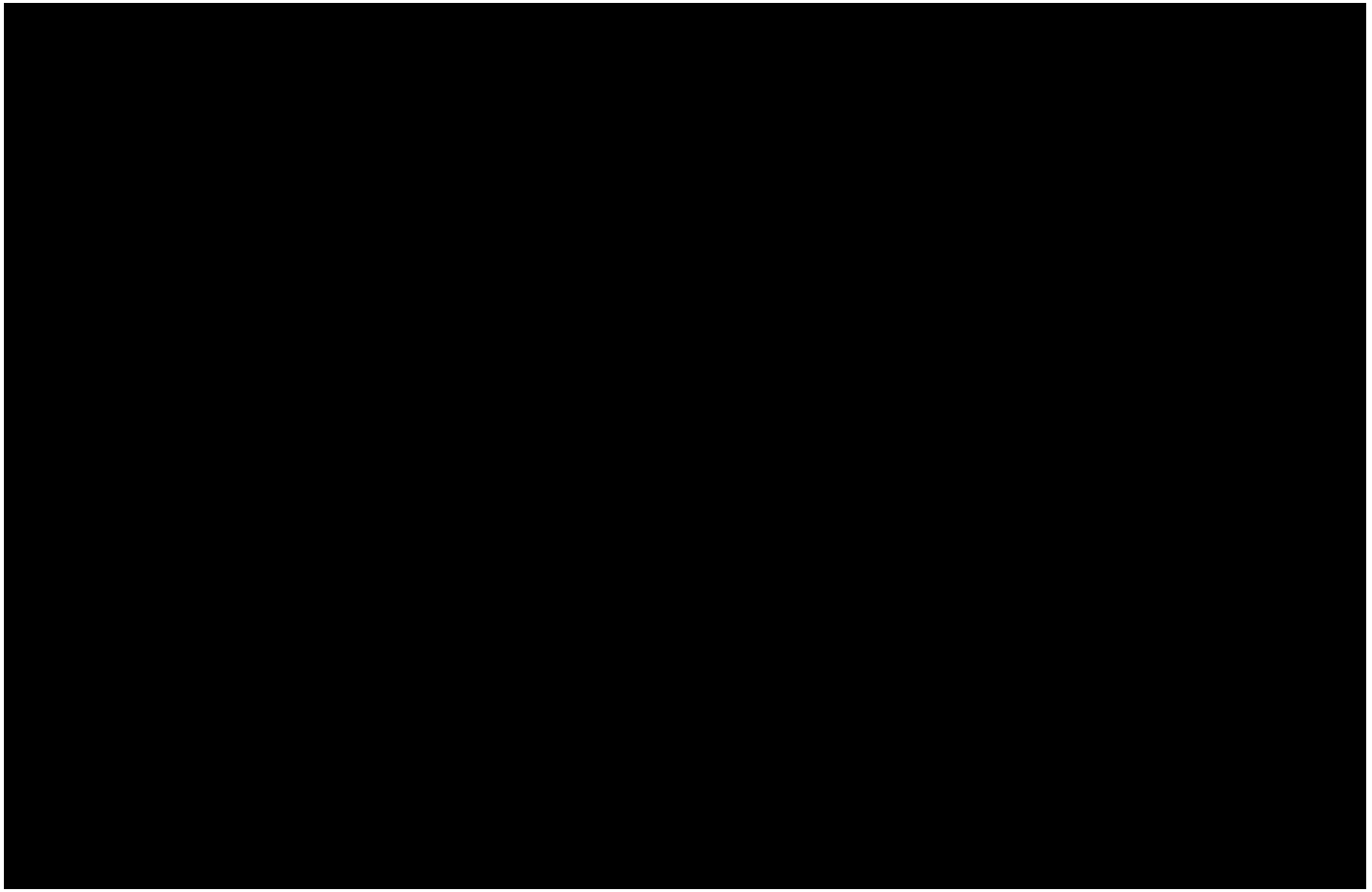


Figure 5: Tornado diagram of the 10 most influential parameters on the ICER against nivolumab

Figure 6: Tornado diagram of the 10 most impactful parameters on the ICER to nivolumab + ipilimumab

Figure 7:Tornado diagram of the 10 most impactful parameters on the ICER to pembrolizumab

Figure 8: Tornado diagram of the most impactful scenarios on the ICER to nivolumab + ipilimumab

Figure 9: Tornado diagram of the most impactful scenarios on the ICER to nivolumab + ipilimumab

Figure 10: Tornado diagram of the most impactful scenarios on the ICER to pembrolizumab

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1 EAG AND COMPANY PFS AND OS CURE MODEL OUTCOMES (POST TECHNICAL ENGAGEMENT)

1.1 EAG revisions fully accepted by the company

This appendix contains company and EAG revised base case (post TE) proportions of patients 'cured' before progression, after progression and overall as a result of changes to the modelling of PFS and OS. The company's post TE base case PFS and OS modelling include two of the revisions proposed in the EAR:

- R1) investigator assessed RELATIVITY-047 trial PFS data
- R3) constant HRs from the company's adjusted ITC for nivolumab+ipilimumab (OS/PFS).

1.2 Proportion of patients 'cured' in company updated base case

In the company base case, it is implicitly assumed that patients can potentially experience 'cure' after they have progressed following treatment in the first-line setting as the estimated cured proportions for OS is greater than that for PFS for each of the treatments in the analysis (more details of this analysis are given in Section 6.2 of the EAR). Further, at least twice as many patients receiving nivolumab-relatlimab in the first line setting go on to experience 'cure' following subsequent treatment than patients treated with any of the comparators in the company's updated base case (Table 1). This implies that i) subsequent therapies have the potential to result in a better response in some patients with worse disease than did the first-line therapies in those same patients before progression, and ii) the proportion of patients statistically 'cured' after subsequent therapy would differ substantially depending on the initial treatment they received. The EAG considers both of these assumptions to be counter-intuitive and to require justification.

Table 1 Proportion of patients 'cured': company updated base case, and EAG combined PFS, OS, NMA and ITC revisions for all treatments (updated from EAR, Table 44)

Treatment	Proportion of patients 'cured'*					
	Company updated base case			EAG PFS, OS, NMA and ITC revisions		
	Before progression	After progression	All patients	Before progression	After progression	All patients
Nivolumab-relatlimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab+ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* 'Cure' proportion defined as the time from which background mortality hazards are used in the model
Note: The EAG corrected an error during calculation of the proportions given in Table 1; 'After progression' and 'All patients' values differ slightly from Table 44 in the EAR. This error does not affect the ICER calculations.
EAG=External Assessment Group; ITC=indirect treatment comparison; OS=overall survival; NMA=network meta-analysis; PD= progressed disease; PFS=progression-free survival

EAG POST-ACM1 CONFIDENTIAL APPENDIX

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab-relatlimab for untreated unresectable or metastatic melanoma [ID1688]

EAG response to NICE requests following ACM1. Cost effectiveness results generated using discounted prices for nivolumab-relatlimab, nivolumab, pembrolizumab, ipilimumab, dabrafenib, trametinib, encorafenib and binimetinib

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Completed 20 October 2023

COMPANY COMMERCIAL IN CONFIDENCE DATA AND COMPARATOR COMMERCIAL IN CONFIDENCE DATA REDACTED

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This appendix contains cost effectiveness results for four analyses requested by NICE following Appraisal Committee 1.

For the comparison of nivolumab-relatlimab versus nivolumab:

- the same proportions on subsequent treatments in the nivolumab-relatlimab arm and nivolumab arm for BRAF wildtype (ipilimumab: 24.59%; clinical trials; 36.89%) (Table 1)
- the same proportions on subsequent treatments in the nivolumab-relatlimab and nivolumab arm for BRAF wildtype (ipilimumab: 20%; chemotherapy or clinical trials: 41.48%) (Table 2)

For the comparison of nivolumab-relatlimab versus pembrolizumab:

- pembrolizumab efficacy set equal to nivolumab efficacy (EAG revision R2) plus the same proportions on subsequent treatments in the nivolumab-relatlimab arm and pembrolizumab arm for BRAF wildtype (ipilimumab: 24.59%; clinical trials: 36.89%) (Table 3)
- pembrolizumab efficacy set equal to nivolumab efficacy (EAG revision R2) plus the same proportions on subsequent treatmentsin the nivolumab-relatlimab and pembrolizumab arm for BRAF wildtype (ipililumab: 20%; chemotherapy or clinical trials: 41.48%) (Table 4)

These results have been generated using the company model submitted during Technical Engagement. Results have been generated using the confidential Patient Access Scheme prices for nivolumab-relatlimab, nivolumab, ipilimumab, dabrafenib, trametinib, encorafenib and binimetinib, the CAA price for pembrolizumab, and the eMIT price for dacarbazine.

Table 1 Nivolumab-relatlimab versus nivolumab: company post-TE base case, nivolumab-relatlimab subsequent treatment proportions for BRAF wild type used in both arms (24.59% ipilimumab and 36.89% chemotherapy or clinical trials)

Analysis	Nivolumab-relatlimab		Nivolumab		Incremental		ICER/QALY
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; QALY=quality adjusted life year; TE=technical engagement

Table 2 Nivolumab-relatlimab versus nivolumab: company post-TE base case, same subsequent treatment proportions for BRAF wild type used in both arms (20% ipilimumab and 41.48% chemotherapy or clinical trials)

Analysis	Nivolumab-relatlimab		Nivolumab		Incremental		ICER/QALY
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; QALY=quality adjusted life year; TE=technical engagement

Table 3 Nivolumab-relatlimab versus pembrolizumab: company post-TE base case, pembrolizumab efficacy=nivolumab efficacy, nivolumab-relatlimab subsequent treatment proportions for BRAF wild type used in both arms (ipilimumab: 24.59%; chemotherapy or clinical trials: 36.89%)

Analysis	Nivolumab-relatlimab		Pembrolizumab		Incremental		ICER/QALY
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; QALY=quality adjusted life year; TE=technical engagement

Table 4 Nivolumab-relatlimab versus pembrolizumab: company post-TE base case, pembrolizumab efficacy=nivolumab efficacy, same subsequent treatment proportions for BRAF wild type used in both arms (ipilimumab: 20% ipilimumab; chemotherapy or clinical trials 41.48%)

Analysis	Nivolumab-relatlimab		Pembrolizumab		Incremental		ICER/QALY
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Probabilistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; QALY=quality adjusted life year; TE=technical engagement