NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Nivolumab plus ipilimumab for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nivolumab plus ipilimumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: February 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by consultees, the final draft guidance may be used as the basis for NICE's guidance on using nivolumab plus ipilimumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

Closing date for comments: 3 March 2025

Second evaluation committee meeting: 13 March 2025

Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Nivolumab plus ipilimumab should not be used for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency in adults.

1.2 This recommendation is not intended to affect treatment with nivolumab plus ipilimumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

What this means in practice

Nivolumab with ipilimumab is not required to be funded in the NHS in England for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency in adults. It should not be used routinely in the NHS in England.

This is because the available evidence does not suggest that nivolumab with ipilimumab offers value for money.

Why the committee made these recommendations

Usual treatment for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency in adults is pembrolizumab or chemotherapy.

Clinical trial evidence shows that nivolumab with ipilimumab increases how long people have before their cancer gets worse compared with chemotherapy. It has not been directly compared in a clinical trial with pembrolizumab, but indirect comparisons suggest that it increases how long people have before their cancer gets

worse compared with pembrolizumab. There is no evidence available to show whether nivolumab with ipilimumab increases how long people live compared with chemotherapy or pembrolizumab.

There are uncertainties in the economic model. This is because of the assumptions used and the way the modelling was done. Also, the cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. So, nivolumab with ipilimumab should not be used for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency.

2 Information about nivolumab plus ipilimumab

Anticipated marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol-Myers-Squibb) with ipilimumab (Yervoy, Bristol-Myers-Squibb) is indicated for the 'first-line treatment of unresectable or metastatic colorectal cancer' in 'adult patients with mismatch repair deficient or microsatellite instability-high colorectal cancer'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for nivolumab.

Price

2.3 Nivolumab costs £2,633 for a 240 mg vial and ipilimumab costs £3,750 for a 50 mg vial (excluding VAT; BNF online accessed January 2025).

2.4 The company has a commercial arrangement. This makes nivolumab plus ipilimumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Bristol-Myers-Squibb, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Mismatch repair deficiency and microsatellite instability

3.1 Colorectal cancer starts in the lining of the large intestine (colon and rectum). Metastatic colorectal cancer occurs when the cancer spreads beyond the large intestine and nearby lymph nodes. Unresectable colorectal cancer may be locally advanced or metastatic and cannot be treated surgically. Mutations can cause deficient mismatch repair (dMMR) of DNA in some unresectable or metastatic colorectal cancer. Mismatch repair corrects errors that occur during DNA replication, so dMMR can lead to mutations and the accumulation of DNA microsatellites (repetitive DNA sequences). This causes them to become unstable, resulting in cancerous tumours with high microsatellite instability (MSI-H). About 4% to 5% of people with metastatic colorectal cancers have biomarkers for MSI-H or dMMR. These are associated with a poorer prognosis and a greater risk of death than metastatic colorectal cancer without these biomarkers. NICE guideline NG151 recommends that everyone with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry to detect dMMR and polymerase chain reaction to detect MSI biomarkers.

Unmet need

3.2 General symptoms associated with metastatic colorectal cancer may include rectal bleeding, abdominal pain, diarrhoea, constipation or both, abdominal bloating, weight loss, tiredness and breathlessness. If the bowel has also become obstructed from the primary tumour, symptoms may also include cramping, constipation and vomiting. The patient expert

explained that a diagnosis of dMMR or MSI-H metastatic colorectal cancer affects quality of life, both physically and psychologically. This is particularly so for people whose cancer is diagnosed at later stages, when it is harder to treat and there is a low chance of survival. The clinical experts explained that unresectable locally advanced colorectal cancer can also be very hard to treat. Depending on the location of the tumour, it can have an equally poor prognosis as metastatic colorectal cancer. They explained that effective treatment options that shrink the tumour, potentially allowing surgical resection, would be very welcome. This is because surgical resection improves the chance of long-term survival. The patient expert explained that chemotherapy is associated with substantial adverse effects that can have a big impact on quality of life. They added that immunotherapies are generally better tolerated by people with metastatic colorectal cancer. But, because of a lack of treatment options, people with the condition are often fearful of losing response to treatment and exhausting all current treatment options. The committee concluded that people with the condition and clinicians would welcome new treatment options.

The treatment pathway

3.3 Treatment options in unresectable or metastatic colorectal cancer with dMMR or MSI-H depend on the availability of genomic test results. Pembrolizumab is currently the preferred first-line treatment option, in line with NICE's technology appraisal on pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA709). The clinical experts explained that the European Society for Medical Oncology (ESMO) guidelines also recommend pembrolizumab for first-line therapy in metastatic colorectal cancer with dMMR or MSI-H. A small proportion of people with metastatic colorectal cancer with dMMR or MSI-H may have chemotherapy at first line instead of pembrolizumab if testing for MMR status is delayed, or if

chemotherapy is the preferred option for a faster response. First-line chemotherapy options include:

- folinic acid plus fluorouracil plus oxaliplatin (FOLFOX)
- folinic acid plus fluorouracil plus irinotecan (FOLFIRI)
- capecitabine plus oxaliplatin (CAPOX)
- capecitabine.

The Cancer Drugs Fund clinical lead explained that the treatment pathways for unresectable and metastatic colorectal cancer are the same. They added that immunotherapy is used off label in locally advanced unresectable colorectal cancer in the NHS. Clinical expert advice received by the EAG suggested that nivolumab plus ipilimumab would be expected to displace some first-line use of pembrolizumab. But it noted that it is not likely to fundamentally change the way in which treatment sequencing is organised because both options are immunotherapies. The committee concluded that pembrolizumab and chemotherapy options are all relevant comparators at first line, but that pembrolizumab is the main comparator.

Clinical trials

CheckMate 8HW

3.4 CheckMate 8HW is an ongoing phase 3, open-label, randomised controlled trial. It investigated the efficacy and safety of nivolumab alone, nivolumab plus ipilimumab, and chemotherapy (including FOLFOX or FOLFIRI, with or without bevacizumab or cetuximab) across all treatment lines. Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent for all arms. For people having nivolumab alone or nivolumab plus ipilimumab, treatment duration was a maximum of 2 years. The company explained that equal effectiveness across chemotherapy combinations could be assumed. So, the chemotherapy arm in CheckMate 8HW was generalisable to the chemotherapy combinations used in the NHS (see section 3.3). People who had disease

progression in the chemotherapy arm and met all crossover criteria were given the option to crossover to nivolumab plus ipilimumab. The EAG noted this reflected clinical practice in the NHS because people who have first-line chemotherapy would be offered an immunotherapy second line (see section 3.3). The primary endpoint in CheckMate 8HW was progression-free survival with blinded independent central review (BICR). The company explained that the primary analysis population for progression-free survival was people with centrally-confirmed dMMR or MSI-H status. But progression-free survival endpoints were also evaluated for everyone who was enrolled based on locally-confirmed dMMR or MSI-H status and randomised. The company further explained that dMMR or MSI-H status can be locally confirmed, or centrally confirmed with greater accuracy at regional laboratories. A key secondary endpoint was overall survival, but overall-survival data from CheckMate 8HW was not presented in the company's submission. The company explained that this was because the trial design meant that the prespecified number of events had not yet been reached, and that the final data cut was expected to be available in 2026. It stated that withholding the interim overall survival analysis was essential to preserve the statistical integrity of the trial, and avoid introducing bias that might lead to incorrect conclusions about overall survival.

The EAG noted that presenting interim analysis of overall survival before full data maturation is common in health technology evaluations. It noted that, at the time of the interim analysis (October 2023), the information fraction was 80%. This suggests that overall-survival data at this time would likely closely parallel the final overall-survival data. The committee concluded that it would have expected to see at least an interim analysis of overall-survival data from CheckMate 8HW. The lack of data on overall survival is a substantial limitation for the clinical-effectiveness analysis of nivolumab plus ipilimumab.

CheckMate 142

3.5 CheckMate 142 was a phase 2, non-randomised, open-label, multicentre trial investigating the efficacy and safety of nivolumab, either alone or with ipilimumab. The primary endpoint in CheckMate 142 was tumour response (best overall response, duration of response and complete response rate) assessed by an investigator. Exploratory endpoints included progression-free survival and overall survival, assessed by BICR. The company presented overall-survival data from a cohort of people with untreated dMMR or MSI-H metastatic colorectal cancer who had nivolumab with ipilimumab in CheckMate 142 (n=45) as supporting evidence. The committee discussed that it would have preferred to see comparative overall-survival data from CheckMate 8HW (see section 3.4). It concluded that overall-survival data from a small cohort of a non-randomised trial was informative but highly uncertain.

Clinical trial results

Progression-free survival

3.6 The clinical-effectiveness data presented for CheckMate 8HW are from an interim analysis (cut-off date 12 October 2023). In everyone with untreated dMMR or MSI-H metastatic colorectal cancer who was randomised, there was a statistically significant and clinically meaningful improvement in progression-free survival assessed by BICR for nivolumab plus ipilimumab compared with chemotherapy. This was also true for people with centrally-confirmed dMMR or MSI-H metastatic colorectal cancer. There was a 12-month progression-free survival rate of 78.7% (95% confidence interval [CI] 71.6 to 84.2) with nivolumab plus ipilimumab (n=171) compared with 20.6% (95% CI 11.2 to 32.0) with chemotherapy (n=84). Median progression-free survival was not reached after 31.6 months of follow up in the nivolumab plus ipilimumab arm. In the chemotherapy arm, median progression-free survival was 5.9 months (95% CI 4.4 to 7.9). The hazard ratio was significantly in favour of

nivolumab plus ipilimumab (0.21, 95% CI 0.14 to 0.32). The clinical experts explained that the improvement in progression-free survival seen in CheckMate 8HW for people who had nivolumab plus ipilimumab compared with chemotherapy was a significant advancement in the treatment of dMMR or MSI-H metastatic colorectal cancer. The committee concluded that, based on the available results from CheckMate 8HW, nivolumab plus ipilimumab improves progression-free survival compared with chemotherapy.

Overall survival

3.7 Overall survival was an exploratory endpoint in CheckMate 142. In the nivolumab plus ipilimumab arm (cohort 3, n=45), the follow up was 64.2 months and, at this point, median overall survival had not been reached. At 60 months, the rate of overall survival was 67%. The committee agreed that the overall-survival results from CheckMate 142 suggested long-term survival benefits with nivolumab plus ipilimumab. But it concluded that the size of the study was too small, and the non-randomised design meant there was high uncertainty about the overall-survival data.

Progression-free survival compared with pembrolizumab

Indirect treatment comparison

3.8 There was no direct clinical trial evidence comparing nivolumab plus ipilimumab with pembrolizumab. So, the company did an indirect treatment comparison to compare progression-free survival assessed by BICR in everyone who was randomised. It did this using 4 approaches:

- a fractional polynomial network meta-analysis (FPNMA)
- an anchored matching-adjusted indirect comparison (MAIC)
- a constant hazard network meta-analysis
- an unanchored MAIC.

The company explained that the most appropriate indirect treatment

comparison was the FPNMA, and that the alternatives were presented as validating analyses only. The EAG agreed with the company. It explained that the FPNMA is a particularly useful approach for capturing non-linear relationships between treatment effects and covariates, and when the assumption of proportional hazards does not hold. The EAG agreed with the company that this was the case in CheckMate 8HW, so estimating a time-varying hazard ratio was most appropriate. The company identified only 1 randomised controlled trial of pembrolizumab that was relevant to the indirect treatment comparison: KEYNOTE-177. This investigated the efficacy of pembrolizumab compared with chemotherapy in locally-confirmed dMMR or MSI-H metastatic colorectal cancer. It was connected in a network with CheckMate 8HW through its chemotherapy arm. The company explained that CheckMate 8HW and KEYNOTE-177 were comparable in terms of:

- their inclusion and exclusion criteria
- the common comparator treatments
- outcome definitions
- study designs.

The 2 trials were also comparable across most of the baseline characteristics assessed. The company explained that the FPNMA showed that hazard of progression or death was reduced with nivolumab plus ipilimumab compared with both chemotherapy and pembrolizumab. This was statistically significant up to 12 months against all treatments, and up to 60 months for all treatments except pembrolizumab. The company noted that, for pembrolizumab, all models predicted a sustained and stabilising hazard ratio of progression or death from month 12 to month 60. The EAG noted that there was a steep reduction in the hazard ratio for nivolumab plus ipilimumab compared with chemotherapy between 0 and 6 months,

highlighting the quick onset of benefit. This reduced hazard function continued up to the end of data collection. But the relative hazard function for nivolumab plus ipilimumab compared with pembrolizumab suggested a more stable relative treatment effect over time. The committee concluded that the indirect treatment comparison results suggested that nivolumab plus ipilimumab improves progression-free survival compared with chemotherapy and pembrolizumab.

Transitivity of the network meta-analysis

3.9 Central testing for dMMR or MSI-H was not done in KEYNOTE-177. All testing was done locally. This differed to CheckMate 8HW, in which the primary analysis population was for people with central confirmation of dMMR or MSI-H status (see section 3.4). Because a centrally confirmed population was not available across all studies in the network, the FPNMA compared progression-free survival assessed by BICR in everyone randomised. The EAG explained that this prevented a robust like-for-like comparison with CheckMate 8HW being done because the principle of the transitivity of the network was violated. In this case, transitivity of the network relied on the generalisability of centrally tested compared with locally tested dMMR or MSI-H status. In CheckMate 8HW, 15% of locally-confirmed cases were determined not to be dMMR or MSI-H when centrally tested, so were excluded from the primary endpoint analysis. The EAG noted that transitivity of the network also relied on the assumption of a class treatment effect for chemotherapy. It noted that there was some heterogeneity of outcomes in the chemotherapy arms of CheckMate 8HW and KEYNOTE-177, but they were similar enough for comparison. The EAG added there were no alternative approaches to resolve this issue because KEYNOTE-177 was the only relevant pembrolizumab study identified for inclusion in the network. The committee concluded that the company's FPNMA was appropriate to assess the treatment effect of nivolumab plus ipilimumab compared with

pembrolizumab. But it acknowledged there were important limitations with the analysis, which meant the results were uncertain.

Validation of progression-free survival estimates

3.10 After its submission, the company provided the EAG with an updated 5-year Kaplan–Meier plot of progression-free survival from CheckMate 8HW. This was assessed by BICR for everyone with centrally-confirmed dMMR or MSI-H status who was randomised to the nivolumab alone and the nivolumab plus ipilimumab arms from CheckMate 8HW. The EAG used this data to validate the extrapolations used in the company's economic model. The EAG was concerned that the observed nivolumab-alone data did not fit well to the modelled progression-free survival for pembrolizumab taken from the FPNMA (see section 3.8). The clinical experts explained that, given the similarities between their modes of action, nivolumab alone would be expected to have similar efficacy to pembrolizumab. The EAG noted that this poor fit between observed and predicted efficacy between nivolumab alone and pembrolizumab suggested that the FPNMA may have underpredicted the efficacy of pembrolizumab. This suggested a larger relative treatment effect for nivolumab plus ipilimumab. So, the EAG did an exploratory analysis and adjusted the hazard ratio for pembrolizumab's modelled time to progression so that it more closely aligned with the nivolumab monotherapy arm. The company did not agree that this was an appropriate approach because it was an ad-hoc exploratory analysis. It explained that the FPNMA was robust and was done in the correct population, so this was the data that should be used in the model. The committee noted that most people in the ad-hoc analysis were having first-line treatment (the exact number is confidential and cannot be reported here). The company suggested that the applicability of the data was reduced because it also included people having later lines of treatment. But the EAG noted that, if this was the case, the updated Kaplan–Meier data for nivolumab plus ipilimumab would also not have

been expected to reflect the modelled time to progression in this arm. But this was not the case. The committee also recalled the uncertainty in the FPNMA results, and noted the views of the clinical experts that nivolumab and pembrolizumab would be expected to have similar outcomes. The committee concluded that the EAG's adjustment to progression-free survival modelling was a more appropriate way to estimate progression-free survival for pembrolizumab.

Economic model

The company's semi-Markov model

3.11 The company used a 3 state semi-Markov model, including progression-free, progressed disease and death states. The company suggested that the semi-Markov approach is appropriate when there is immature overall-survival data, as is currently the case. The progression-free to progressed-disease transition used time-to-progression data from CheckMate 8HW for chemotherapy and nivolumab plus ipilimumab, and from the FPNMA for pembrolizumab. The progression-free to death transition used pre-progression survival data from general population mortality. The progressed-disease to death transition used post-progression survival data from CheckMate 142, and was assumed to be the same for all treatment arms in the model. The EAG noted that, within this model structure, gains in progression-free survival directly equate to a gain in the estimated overall survival. Because overall-survival data was not provided from CheckMate 8HW, the EAG was unable to validate this assumption. It explained that this was a major concern with the company's model. The committee agreed with the EAG that this assumption was a source of substantial uncertainty, but concluded that the model was appropriate for decision making.

Survival model assumptions

Assumption that progression-free survival translates to overall survival

3.12 The company's model assumed equal post-progression survival across all arms in the model (see section 3.9). The EAG highlighted that this means the model assumes that progression-free survival in each arm translates into overall survival. The company suggested that post-hoc correlation analysis between progression-free survival and overall survival from cohort 3 (first-line nivolumab plus ipilimumab) in CheckMate 142 (n=45, median follow up 52.6 months) showed that this was a reasonable assumption. The company also provided validation of its predicted overall survival using data from KEYNOTE-177 and pooled data from cohorts of people having first-line nivolumab plus ipilimumab, or second-line or later nivolumab plus ipilimumab in CheckMate 142. The clinical experts agreed that using progression-free survival as a proxy for overall survival is appropriate when there is a lack of overall-survival data (see section 3.6). The EAG noted that the company's validation of overall-survival predictions compared with CheckMate 142 showed that the model consistently overpredicts overall survival for nivolumab plus ipilimumab when compared with the observed data for pembrolizumab from KEYNOTE-177. The EAG also highlighted some immature safety endpoint death data from CheckMate 142 (this data is considered confidential by the company and cannot be reported here). It noted that these results provide some means of additional validation of an overall-survival benefit for nivolumab plus ipilimumab compared with pembrolizumab. But because the data was only reported as total deaths up to 1 point in time, it had limited interpretability compared with Kaplan–Meier data. The EAG emphasised that omitting overall-survival data from the economic model is a major concern that substantially limits analysis of clinical effectiveness. So, the EAG presented a scenario analysis assuming equal overall survival between nivolumab plus ipilimumab and pembrolizumab, which the EAG considered to be equally plausible. The

committee agreed with the EAG that the lack of overall-survival data meant it is difficult to validate the model assumption that gains in progression-free survival will directly translate to gains in overall survival. Also, any conclusions about overall survival have very limited interpretability. It noted that overall-survival data will not be available within the timeframe of this evaluation. So, it would be necessary to rely on the progression-free survival surrogacy presented in the company's economic model. The committee concluded that this was a substantial limitation that contributes a high degree of uncertainty to the cost-effectiveness analysis.

Post-progression survival

3.13 The company's model used overall-survival data from CheckMate 142 in people who had nivolumab plus ipilimumab at first line (cohort 3) or second-line or later (cohort 2) to estimate post-progression survival in all treatment arms. The EAG highlighted that by using the same data for all arms in the model, it was assumed that chemotherapy as second-line treatment (after first-line immunotherapy) was equally effective as second-line immunotherapy (after first-line chemotherapy). The company explained that the assumption of equal efficacy between chemotherapy and nivolumab plus ipilimumab at second line was justified because equal effectiveness of subsequent treatments was previously accepted in TA709. But the EAG noted that at the time of that evaluation nivolumab plus ipilimumab was not available as a subsequent treatment and so this justification is not appropriate for the current evaluation. The EAG highlighted that the company's assumption on post-progression survival in this evaluation did not align with the company's model assumptions in NICE's technology appraisal on nivolumab and ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency (TA716). In TA716, the company proposed that nivolumab plus ipilimumab was more effective than chemotherapy as second-line treatment. At the EAG's request, the company presented a

scenario analysis using data from cohort 2 of CheckMate 142 to inform post-progression survival after chemotherapy. The company used an exponential curve fit to this data. The EAG explained that this scenario better reflects the expectation of improved survival with nivolumab plus ipilimumab compared with chemotherapy at second line. But it also noted that the company did not sufficiently justify selecting the exponential curve and so the EAG could not fully critique this choice of approach. But the EAG preferred this scenario for its own base case. The committee agreed with the EAG that the company's scenario was more clinically plausible and concluded that it was appropriate.

Subsequent treatments

3.14 The company used a clinical advisory board to inform subsequent therapy type in the economic model. After having nivolumab plus ipilimumab or pembrolizumab at first line, people would be offered chemotherapy (FOLFOX) in line with the lowest-cost chemotherapy accepted in TA716. After chemotherapy at first line, people would be offered nivolumab plus ipilimumab. The EAG noted that pembrolizumab is recommended by NICE at second line only if people cannot have nivolumab plus ipilimumab (see NICE's technology appraisal on pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency). The EAG noted that nivolumab plus ipilimumab is more effective than other available second-line options, but the model only accounts for the additional cost of having nivolumab plus ipilimumab. It explained that by assuming everyone has nivolumab plus ipilimumab after chemotherapy, and not incorporating the impact of subsequent treatments on survival, a bias is created in favour of nivolumab plus ipilimumab treatment arm. So, the EAG assumed that after first-line chemotherapy 42% of people had pembrolizumab rather than nivolumab plus ipilimumab, based on information from the NHS Cancer Drugs Fund clinical lead. But the NHS Cancer Drugs Fund clinical lead later referred to data showing that 56% of

people have pembrolizumab and 40% have nivolumab plus ipilimumab after chemotherapy in NHS clinical practice. They explained that pembrolizumab is less toxic than nivolumab and ipilimumab and so may be favoured in older people. A small proportion of people would have chemotherapy because of contraindications to immunotherapy. The committee agreed that it was appropriate to model the effectiveness and costs of subsequent treatments in line with the treatments that would be expected to be used at second line in NHS clinical practice. This included assuming the following proportions for subsequent treatments in the chemotherapy arm:

- 56% pembrolizumab
- 40% nivolumab plus ipilimumab
- 2.2% FOLFIRI
- 1.8% FOLFOX.

It would also be appropriate to assume that FOLFOX would be the only subsequent treatment after first-line nivolumab plus ipilimumab or pembrolizumab, in line with NHS clinical practice.

Other model assumptions

Time to progression

3.15 The company model applied each survival curve for the full model time horizon and did not explore the potential for treatment-effect waning. The EAG noted that that the treatment effect of nivolumab plus ipilimumab compared with pembrolizumab reduces over time but remains positive for the entire modelled horizon. Clinical advice to the EAG stated that nivolumab plus ipilimumab would be expected to show a greater effect at first, but that this would likely be within the first year of treatment only and would not be expected to continue indefinitely over the whole time horizon. This assumption is also supported by the fact that progression events are usually seen within the first 2 years of treatment. The EAG

instead preferred to assume that the hazards for nivolumab plus ipilimumab and pembrolizumab were equal after 2 years for its base case. The committee considered the plausibility that nivolumab plus ipilimumab would continue to show increasing clinical benefit over pembrolizumab for the entire time horizon. It agreed with the EAG that it was not likely to be clinically plausible and concluded that equal hazards for nivolumab plus ipilimumab and pembrolizumab should be assumed after 2 years of treatment.

Time to treatment discontinuation

3.16 In its evidence submission, the company explained that it had used the Kaplan–Meier data from CheckMate 8HW to model time to treatment discontinuation (TTD) for nivolumab plus ipilimumab and chemotherapy. But the EAG noted that the Kaplan–Meier data was not present in the model, and that the company had instead used progression-free survival to model TTD for these treatments. The EAG noted that this is not ideal because it does not allow for treatment after progression, which was allowed in CheckMate 8HW and KEYNOTE-177. For pembrolizumab, Kaplan–Meier TTD data was not available from KEYNOTE-177, so TTD was assumed to be same as for nivolumab plus ipilimumab. The EAG stated that similar duration of treatment for pembrolizumab and nivolumab plus ipilimumab is not logical if assuming nivolumab plus ipilimumab is more effective. It further noted that although a naive comparison showed that the TTD for nivolumab plus ipilimumab and pembrolizumab was similar, the chemotherapy arm in KEYNOTE-177 has a longer duration of treatment than in CheckMate 8HW. The EAG explained that this makes a naive comparison biased in favour of nivolumab plus ipilimumab, because the treatment duration (and associated costs) with pembrolizumab will be overestimated relative to nivolumab plus ipilimumab. If an indirect treatment comparison had been used instead of a naive comparison, it would expect to see a shorter TTD for pembrolizumab. The company explained that the way TTD was accounted for differs between

CheckMate 8HW and KEYNOTE-177 in terms of whether people still on treatment are censored, and so they did not offer any scenarios to further explore this issue. But the EAG noted that the data presented is the mean duration of treatment data, which uses the same definition in both trials, so it is not affected by censoring. The EAG explored this issue by applying the hazard ratio used for time to progression to the TTD Kaplan–Meier curve for nivolumab plus ipilimumab. It explained that this was appropriate because treatment duration is linked to time to progression, because people will usually stop treatment after progression. The clinical experts warned against comparing across KEYNOTE-177 and CheckMate 8HW to determine TTD. This was because these trials were done at different times and knowledge about the clinical benefits of staying on an immunotherapy has increased over that time, which may have influenced decisions to stop treatment. The committee considered the company's approach and the EAG's alternative assumption. It concluded that it was not appropriate to assume equal TTD for nivolumab plus ipilimumab and pembrolizumab because of the risk of bias in the naive comparison between trials and the clinical plausibility of this assumption. So, it preferred the EAG's alternative assumption of applying the hazard ratio used for time to progression to the TTD Kaplan–Meier curve for nivolumab plus ipilimumab.

Resource costs

3.17 The resource use estimates for the progression-free and progressed-disease states were derived from those applied during TA709. Clinical advice to the EAG suggested that these costs were high compared with those used in other oncology evaluations. But the EAG accepted there was a high degree of inconsistency between different evaluations. It suggested that the costs used for best supportive care taken from Färkkilä (2015) were not appropriate because these costs related to palliative care when all active treatment options have been exhausted (originally used in NICE's technology appraisal guidance on cetuximab and panitumumab for

previously untreated metastatic colorectal cancer to represent people having third-line treatment). The EAG noted that palliative care costs had been applied to the entire post-progression period, regardless of whether active second-line treatment was being used. It explained that in the UK, most people are not usually referred to palliative care until the last few weeks of life. The EAG also questioned whether the assumption that visits with a consultant would happen once every 2 weeks on top of drug administration for the entire progression-free period was appropriate. Clinical expert advice to the EAG suggested that, for immunotherapies such as nivolumab and pembrolizumab, clinical consultations are usually scheduled to align with treatment provision. Once people have finished active treatment with an immunotherapy they would typically be seen and scanned every 3 months for 1 to 2 years, then once every 6 months, until discharge at 5 years if their cancer has not progressed. For chemotherapy, clinical advice to the EAG was that people would be seen before each cycle of chemotherapy (every 2, 3 or 4 weeks depending on the type). Once active treatment stopped the same rules would be used as for immunotherapies. The EAG also explained that it preferred to apply increased costs for subsequent lines of treatment using a payoff approach, in line with how drug and administration costs are applied. It also aligned resource costs for first- and second-line treatment. The committee considered the appropriateness of the company's and EAG's implementation of resource costs in the model. It concluded that neither the EAG or company's resource use exactly reflected clinical practice, but the EAG's assumptions more closely reflected the costs that would be relevant to the NHS. So, it preferred to use the EAG's implementation of resource costs.

Cost-effectiveness estimates

Acceptable ICER

3.18 NICE's manual on health technology evaluation notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER, as well as aspects that relate to uncaptured benefits. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented, but may also consider if the model has not captured any health benefits which should be reflected in the acceptable ICER.

The committee noted the high level of uncertainty, most notably in:

- the treatment effect because of lack of overall-survival data (see section 3.4)
- the FPNMA because of violation of transitivity and class treatment effect assumptions (see section 3.9)
- whether progression-free survival can be assumed to translate to overall survival (see section 3.12).

The clinical experts explained that current clinical experience in people with dMMR or MSI-H metastatic colorectal cancer suggests that up to about one-third of people who had had unresectable disease could have resectable disease after treatment with nivolumab plus ipilimumab. This could allow them to have potentially curative surgery and improve the chance of long-term survival (see section 3.2). The committee considered this to be a clinical benefit that had not been captured in the economic model. So, taking both the high levels of uncertainty and the uncaptured benefits into account, the committee concluded that an acceptable ICER would be around £25,000 per QALY gained.

Committee's preferred assumptions

3.19 The committee agreed that its preferred assumptions to compare nivolumab plus ipilimumab with pembrolizumab and chemotherapy included:

- Application of a hazard ratio to the modelled time to progression curve for pembrolizumab to improve visual fit to the 5-year Kaplan–Meier progression-free survival data for nivolumab alone (see section 3.10).
- Post-progression survival for people after first-line chemotherapy taken from exponential fit to cohort 2 of CheckMate 142 overall survival to reflect expectation of improved survival with nivolumab plus ipilimumab (see section 3.13).
- Using data from the Cancer Drugs Fund clinical lead on subsequent treatment use after immunotherapy and chemotherapy to inform the subsequent treatments used in the model (see section 3.14).
- Treatment effect from the FPNMA only applies to the first 2 years of the model and after this hazards are equal for pembrolizumab and nivolumab plus ipilimumab (see section 3.15).
- Time on treatment for pembrolizumab assumed to be lower than time on treatment for nivolumab plus ipilimumab, based on applying the hazard ratio used for time to progression to the TTD Kaplan–Meier curve for nivolumab plus ipilimumab (see section 3.16).
- The EAG's preferred assumptions for resource use:
  - oncologist visits aligning with treatment administration visits, then tapering once people are off treatment, and stopping when people are discharged at 5 years
  - costs for second-line treatment aligning with those for first-line treatment
  - palliative care costs aligned to people having palliative care in line with UK practice

- costs for subsequent lines of treatment applied using a payoff approach (see section 3.17).

The committee also agreed with the following minor changes to the company's model preferred by the EAG:

- Health Survey England data rather than trial body weight used to calculate wastage
- using trial data rather than market share to model the split of treatments included in the chemotherapy comparator
- no half-cycle correction for TTD.

When taking into account all of the committee's preferred assumptions, the ICER for nivolumab plus ipilimumab compared with pembrolizumab and chemotherapy was above the committee's preferred threshold (£25,000 per QALY gained). The exact ICERs include confidential discounts for treatments in the pathway and so cannot be reported here.

Cancer Drugs Fund

3.20 Having concluded that nivolumab plus ipilimumab was not recommended for routine commissioning, the committee considered whether a recommendation through the Cancer Drugs Fund could be appropriate. It agreed that given the high level of uncertainty, particularly relating to the lack of overall-survival data, further data collection could have resolved some of the remaining uncertainties. But the company did not submit a proposal for the Cancer Drugs Fund, so the committee was unable to make a recommendation through this route.

Other factors

Equality

3.21 The committee did not identify any equality issues.

Conclusion

Recommendation

3.22 The committee took into account its preferred assumptions and the key uncertainties in the model. It concluded that the most plausible ICER for nivolumab plus ipilimumab compared with chemotherapy and pembrolizumab was above its preferred ICER threshold. So, nivolumab plus ipilimumab is not recommended.

4 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology appraisal by the highly specialised technologies evaluation committee. The highly specialised technologies evaluation committee and the 4 technology appraisal committees are standing advisory committees of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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Technical leads

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Technical adviser

Jeremy Powell
Project manager

Emily Crowe
Associate director

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