NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

1.1 Nivolumab plus ipilimumab can be used, within its marketing authorisation, as an option for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency in adults.

1.2 Nivolumab plus ipilimumab can be used if the company provides it according to the commercial arrangements (see section 2).

What this means in practice

Nivolumab plus ipilimumab must be funded in the NHS in England for untreated unresectable or metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency in adults, if it is considered the most suitable treatment option. Nivolumab plus ipilimumab must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that nivolumab plus ipilimumab provides clinical benefits and value for money for this population, so it can be used routinely across the NHS.

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, compared with chemotherapy, nivolumab plus ipilimumab increases how long people have before their cancer gets worse and how long they live. Indirect comparisons suggest that nivolumab plus ipilimumab also increases how long people have before their cancer gets worse and how long they live compared with pembrolizumab.

The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, nivolumab plus ipilimumab can be used.

2 Information about nivolumab with ipilimumab

Marketing authorisation indication

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

Dosage in the marketing authorisation

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

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 March 2025).

2.4 The company has commercial arrangements (a simple discount patient access scheme for nivolumab and a patient access scheme plus commercial access agreement for ipilimumab). These make nivolumab

and ipilimumab available to the NHS with a discount. 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 is 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's diagnostics guidance on molecular testing strategies for Lynch syndrome in people with colorectal cancer recommends that everyone with colorectal cancer should be offered testing when first diagnosed, using immunohistochemistry to detect dMMR or polymerase chain reaction to detect MSI.

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 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 than chemotherapy by people with unresectable or 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 treatment options. The committee concluded that people with the condition and clinicians would welcome new first-line 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. A small proportion of people with unresectable or

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. The committee concluded that pembrolizumab and chemotherapy are both 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. The people included had locally confirmed dMMR or MSI-H unresectable or metastatic colorectal cancer. 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 dMMR or MSI-H status can be locally or centrally confirmed, and that central confirmation is more accurate. It 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 (intention-to-treat population). A key secondary endpoint was overall survival.

After draft guidance consultation, the company provided immature overall-survival data from a data cut from September 2024. This included overall-survival outcomes for nivolumab plus ipilimumab compared with chemotherapy at first line and nivolumab plus ipilimumab compared with nivolumab alone in all treatment lines. The populations reported from the September 2024 data cut all had locally confirmed dMMR or MSI-H unresectable or metastatic colorectal cancer.

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. It included people with locally confirmed dMMR or MSI-H unresectable or metastatic colorectal cancer. 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 (labelled cohort 3 in the study) of people with untreated dMMR or MSI-H unresectable or metastatic colorectal cancer who had nivolumab plus ipilimumab in CheckMate 142 (n=45) as supporting evidence. The committee concluded that overall-survival data from a small cohort of a non-randomised trial was informative but highly uncertain. At consultation, one clinical expert stated that data from both trials are informative and results in both trials are consistent for all efficacy endpoints.

Clinical trial results

Progression-free survival

3.6 The progression-free survival data presented for CheckMate 8HW was from an interim analysis (cut-off date 12 October 2023). In people with untreated dMMR or MSI-H unresectable or metastatic colorectal cancer who were randomised (locally confirmed), there was a statistically significant and clinically meaningful improvement in progression-free survival. This was 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 untreated dMMR or MSI-H unresectable or 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, in the population of interest, the size of the study was small. Also, it was non-comparative (single-arm, nivolumab plus ipilimumab) and the non-randomised design meant there was high uncertainty about the overall-survival data. In response to the draft guidance consultation, the company provided immature overall-survival data from CheckMate 8HW (September 2024 data cut). Overall-survival data was presented for people with untreated locally confirmed dMMR or MSI-H unresectable or metastatic colorectal cancer treated at:

- first line with nivolumab plus ipilimumab compared with chemotherapy (n=303)
- any line with nivolumab plus ipilimumab compared with nivolumab alone(n=707).

This data is confidential and cannot be reported here. The committee concluded that the overall-survival data from CheckMate 8HW reduced the amount of uncertainty about overall survival for people having nivolumab plus ipilimumab.

Progression-free survival compared with pembrolizumab and chemotherapy

3.8 There was no direct clinical trial evidence comparing nivolumab plus ipilimumab with pembrolizumab. So, the company did 4 indirect treatment comparisons for progression-free survival for nivolumab plus ipilimumab compared with pembrolizumab. The company and the EAG agreed that the fractional polynomial network meta-analysis (FPNMA) was the 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 untreated 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 design

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 60 months. Because only local testing for dMMR or MSI-H status was done in KEYNOTE-177, the intention-to-treat population in CheckMate 8HW (the locally confirmed population) was included in the network. The company noted that central confirmation of dMMR or MSI-H status is more accurate than local testing. So, a proportion of people were included in the locally confirmed population who had mismatch repair proficient or microsatellite stable (pMMR or MSS) disease. The

company explained that pMMR or MSS disease does not respond to immuno-oncology therapies such as nivolumab, ipilimumab and pembrolizumab. So, progression-free survival outcomes are worse for locally confirmed compared with centrally confirmed populations. The company explained that this meant that results from the FPNMA may have underestimated the effect of nivolumab plus ipilimumab compared with pembrolizumab. The EAG noted that, by not being able to limit the NMA to the centrally confirmed population, there was a risk of non-differential ascertainment bias. This reduced the reliability of the results. It also noted that transitivity relied on assuming a class effect for chemotherapy and that the heterogeneity in chemotherapy arms across studies added a level of uncertainty to the results. The committee concluded that the FPNMA results suggested that nivolumab plus ipilimumab improves progression-free survival compared with chemotherapy and pembrolizumab. But it also concluded that there were important limitations with the FPNMA, which may have affected the reliability of the results.

Economic model

The company's semi-Markov model

3.9 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. The progression-free to progressed-disease transition used time-to-progression data from CheckMate 8HW for nivolumab plus ipilimumab and chemotherapy, and from the FPNMA for pembrolizumab. The progression-free to death transition used preprogression survival data from general population mortality. The progressed-disease to death transition used postprogression survival data from different trials to estimate differences in survival associated with different postprogression treatments. The EAG noted that, within this model structure, gains in

progression-free survival translate to a gain in the estimated overall survival (see section 3.10). It explained that it would have been most appropriate to incorporate overall-survival data directly into the model. The committee agreed that the model was appropriate for decision making, but it would have preferred to have seen overall-survival data included in the model.

Survival model assumptions

Assumption that progression-free survival translates to overall survival

3.10 Overall-survival data was not provided in the initial company submission. Instead, the company provided evidence to support using progression-free survival as a surrogate endpoint for overall survival. This included a 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 5 2.6 months). 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.

In response to the draft guidance consultation, the company provided immature overall-survival data from CheckMate 8HW (see section 3.7). The company used this data to further validate the assumption in the model that progression-free survival translates to overall survival. It did this by comparing the modelled overall-survival outcomes for nivolumab plus ipilimumab, pembrolizumab and chemotherapy with the observed overall-survival data. The clinical experts noted that pembrolizumab and nivolumab would be expected to have similar outcomes because they have the same mechanism of action. So, it was appropriate to validate pembrolizumab model outcomes using observed nivolumab-alone data from CheckMate 8HW. The EAG explained that the overall-survival data

resolved the uncertainty around the treatment effect of nivolumab plus ipilimumab compared with chemotherapy. But it added that it did not fully address the uncertainty of the treatment effect compared with pembrolizumab. This was because of the fit of the observed overall-survival data for nivolumab plus ipilimumab and nivolumab alone compared with the modelled outcomes for nivolumab plus ipilimumab and pembrolizumab. The clinical experts explained that using progression-free survival as a surrogate for overall survival was appropriate. This was because the treatment effects of nivolumab plus ipilimumab are expected to be maintained long term. The clinical experts also noted that there is an increasing number of people with unresectable disease who are able to have surgery after treatment with nivolumab plus ipilimumab. This may lead to improved overall survival than seen in the clinical trial.

The committee concluded that the overall-survival data validated the assumption that progression-free survival gains resulted in overall-survival gains. It also concluded that the immature overall-survival data from CheckMate 8HW helped resolve some uncertainty around overall-survival estimates in the model. But, it noted the differences in modelled overall-survival estimates compared with observed results. So, it concluded that there was still uncertainty in the modelled overall-survival estimates.

Time to progression for pembrolizumab

3.11 The company model included time to progression for pembrolizumab derived from the progression-free survival hazard ratio from the FPNMA. The EAG stated that the observed progression-free survival data for nivolumab alone from CheckMate 8HW did not fit well to the modelled progression-free survival for pembrolizumab taken from the FPNMA. The clinical experts raised that they would expect the efficacy of pembrolizumab and nivolumab to be similar (see section 3.10). At the first committee meeting, the EAG provided an exploratory analysis with an adjusted hazard ratio so that pembrolizumab progression-free survival

more closely aligned with the nivolumab-alone observed data.

In response to the draft guidance consultation, the company stated that the EAG's approach was inappropriate and that it overestimated pembrolizumab progression-free survival. It explained that this was, in part, because the nivolumab-alone observed data that the EAG had used to estimate the adjustment factor was from a centrally confirmed population. This population was expected to have better outcomes than the locally confirmed population in the FPNMA (see section 3.8). The company also noted that the nivolumab-alone data was for people at all lines of treatment and not only at first line. The clinical experts stated that they would expect the line at which a person has the treatment to affect the treatment response. The company maintained its original approach in its base case and presented 2 scenarios using nivolumab-alone data as a proxy for pembrolizumab. The first scenario adjusted the nivolumab plus ipilimumab time-to-progression curve. It did this using the progression-free survival hazard ratio for nivolumab plus ipilimumab compared with nivolumab-alone data in CheckMate 8HW (published in Andre et al. (2025) and referred to as the Andre hazard ratio approach). The second scenario extrapolated nivolumab-alone data from CheckMate 8HW using a generalised gamma curve.

The EAG noted that all approaches showed differences to the observed overall-survival data. But it preferred to use the Andre hazard ratio approach even though the other 2 approaches showed fewer differences to the observed overall-survival data. This was because the Andre hazard ratio approach avoided overestimating the difference between nivolumab plus ipilimumab and pembrolizumab. The committee noted that all methods were limited because of over and underestimation in the modelling compared with the observed data. But it concluded that it preferred the Andre hazard ratio approach to estimate time to progression

for pembrolizumab because it avoided overestimating the difference between nivolumab plus ipilimumab and pembrolizumab.

Long-term relative treatment effect difference

3.12 The company model applied each survival curve for the full model time horizon. The EAG noted that that the modelled treatment effect of nivolumab plus ipilimumab compared with pembrolizumab reduced over time but remained 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 this would not be expected to continue indefinitely over the whole time horizon. At the first committee meeting, the EAG instead preferred to assume that the hazards for nivolumab plus ipilimumab and pembrolizumab were equal after 2 years for its base case. So, the EAG's model assumed that, from 2 years, the hazards did not diverge anymore, meaning that the long-term relative treatment effect was maintained.

In response to the draft guidance consultation, the company stated that the progression-free survival data at 4 years from CheckMate 8HW inferred that there was stability in clinical efficacy beyond 2 years. The EAG agreed with this but suggested that longer-term data would be needed to determine when the relative difference should be assumed to be equal. The EAG noted that long-term relative treatment effect was a concern because the overall-survival data was not included in the model from which a long-term relative treatment effect could be shown. The EAG noted that, without evidence, making a decision on when the relative treatment effect will become equal was difficult. So, it removed any treatment effect waning from its base case at the second committee meeting. The clinical experts stated that they would expect the relative treatment effect to be maintained.

The committee noted that there was limited long-term data, so this

remained an uncertainty. It recalled concerns with the modelled overall-survival data (see section 3.11). The committee discussed that, without long-term survival data, it was difficult to decide between choosing a timepoint at which to introduce equal relative treatment effect or never introducing an equal relative treatment effect. The committee stated that the clinical experts and the CheckMate 8HW study provided some evidence for long-term relative treatment effect difference. But, because of the absence of long-term overall-survival data in colorectal cancer, it was uncertain how long this difference would be observed for. So, the committee agreed that the appropriate approach would be to introduce an equal relative treatment effect at some point in the model. The company explained that, in a trial of people with melanoma, progression-free survival benefits of nivolumab plus ipilimumab compared with nivolumab alone were maintained for 10 years. The EAG noted that melanoma is highly responsive to immunotherapy. This is because of several factors related to its tumour biology and immune microenvironment and that performance of immunotherapies has not been consistent across different tumour types. But the clinical experts confirmed that, in the absence of data in colorectal cancer, they would consider this data from melanoma applicable. The company suggested that there was evidence to support a statistically significant benefit for nivolumab plus ipilimumab compared with pembrolizumab to at least 6 years. So, it provided a scenario analysis implementing an equal relative treatment effect from 6 years, which it considered conservative. The EAG queried this. It highlighted that the FPNMA results suggested statistically significant benefits in progression-free survival between nivolumab plus ipilimumab and pembrolizumab for up to 5 years (see section 3.8). The committee concluded that data from the melanoma population was informative. But the lack of data in metastatic colorectal cancer beyond 5 years meant that it was uncertain when it would be appropriate to assume equal relative treatment effect. It concluded this may be longer than the 6 years that was proposed by the company as a reasonable, but conservative estimate, based on the

evidence in colorectal cancer. So, it agreed that, although it was uncertain, an equal relative treatment effect should be included in the model from 8 years.

Other model assumptions

Time to treatment discontinuation for pembrolizumab

3.13 In its evidence submission, the company used the progression-free survival from CheckMate 8HW to model time to treatment discontinuation (TTD) for nivolumab plus ipilimumab and chemotherapy. 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 was illogical if assuming nivolumab plus ipilimumab is more effective. So, it preferred to estimate TTD for pembrolizumab by applying the hazard ratio used for time to progression to the TTD Kaplan–Meier curve for nivolumab plus ipilimumab. In response to the draft guidance consultation, the company provided nivolumab-alone TTD data from all treatment lines in CheckMate 8HW. It used this TTD data to model time on treatment for pembrolizumab. At the second committee meeting, the EAG stated that this method was much preferred, and the only concern was that nivolumab alone was for all treatment lines, so may not be reflective of first-line treatment. It also explained that the company's approach may have underestimated TTD for pembrolizumab and so could be considered conservative. The committee concluded that the company's updated approach using nivolumab-alone TTD data as a substitute for pembrolizumab TTD was appropriate.

Subsequent treatments

3.14 The company used a clinical advisory board to inform subsequent therapy type in the economic model in its initial submission. After having nivolumab plus ipilimumab or pembrolizumab at first line, it assumed that

people would be offered chemotherapy (FOLFOX) in line with the lowest-cost chemotherapy accepted in NICE's technology appraisal guidance on nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. After chemotherapy at first line, the company assumed that 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 at second line (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 was created in favour of the nivolumab plus ipilimumab treatment arm. The NHS Cancer Drugs Fund clinical lead referred to data on the proportions of subsequent treatments used after first-line chemotherapy in NHS clinical practice. They explained that pembrolizumab is less toxic than nivolumab plus ipilimumab, so may be favoured for older people. One clinical expert stated that, in current practice, 43% of people diagnosed with colorectal cancer are 75 years and older. A small proportion of people would have chemotherapy because of contraindications to immunotherapy. The data showed that the following proportions of subsequent treatments are used after chemotherapy in NHS clinical practice:

- 56% pembrolizumab
- 40% nivolumab plus ipilimumab
- 2.2% FOLFIRI

- 1.8% FOLFOX.

The committee agreed that it was appropriate to model the effectiveness and costs of subsequent treatments in line with the treatments that would be used at second line in NHS clinical practice.

Postprogression survival on subsequent treatments after chemotherapy

3.15 In its submission, 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 postprogression 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 a second-line treatment (after first-line immunotherapy) was equally effective as second-line immunotherapy (after first-line chemotherapy). At the EAG's request, the company presented a scenario analysis using data from cohort 2 of CheckMate 142 to inform postprogression survival after chemotherapy. The company used an exponential curve fit to this data but did not sufficiently justify the choice of curve. So, the EAG could not fully critique this approach, but it did prefer this scenario for its own base case. This was because it better reflected the expectation of improved survival with nivolumab plus ipilimumab compared with chemotherapy at second line. In response to the draft guidance consultation, the company noted that the EAG's model did not align costs and benefits for subsequent treatments after first-line chemotherapy. This biased outcomes in favour of the chemotherapy arm. The company presented a new scenario using data from the following sources to inform postprogression survival after chemotherapy in the model:

- Cohort 2 of CheckMate 142 for nivolumab plus ipilimumab
- KEYNOTE 164 (pembrolizumab for previously treated dMMR or MSI-H advanced colorectal cancer) for pembrolizumab

- CRYSTAL (FOLFOX for previously treated metastatic colorectal cancer) for chemotherapy.

The EAG explained that the company's updated approach was more appropriate. But, it noted that the company continued to assume an exponential curve fit to these data sources, despite the poor model fit. The EAG was concerned about the model fit. But it noted that, when comparing postprogression survival from the model to the observed data, it was likely that the company's approach was conservative. So, it accepted the changes to the model by the company in its updated base case. The committee agreed that it was appropriate to use the data from individual sources to inform postprogression survival after chemotherapy in the model.

Time on subsequent treatment after chemotherapy

3.16 After first-line chemotherapy, the time spent on second-line treatments (nivolumab plus ipilimumab, and pembrolizumab) differed between the company's and EAG's models. The company used median time to discontinuation from CheckMate 8HW, and assumed that nivolumab plus ipilimumab and pembrolizumab would have the same time to discontinuation at second line. The EAG did not agree with using the same time to discontinuation for nivolumab plus ipilimumab and for pembrolizumab. It also noted that it is more appropriate to use mean data rather than medians in economic analysis. To estimate different time to discontinuation for nivolumab plus ipilimumab and pembrolizumab, the EAG preferred to use data from the first-line inputs in the model. Its base case used mean time to discontinuation for first-line nivolumab plus ipilimumab and pembrolizumab from the model to estimate the time on the same treatment after chemotherapy. The EAG noted that this data is not ideal and that it would have preferred to see data for people on subsequent treatment lines, rather than first-line treatment. The committee acknowledged the uncertainties but noted that this would only affect the

comparison of nivolumab plus ipilimumab with chemotherapy. The committee concluded that the EAG's approach was more appropriate because it estimated different times on treatment for different immunotherapies after chemotherapy.

Resource costs

3.17 The resource use estimates for the progression-free and progressed-disease states were derived from those applied during NICE's technology appraisal on pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. Clinical advice to the EAG suggested that these costs were high compared with those used in other oncology evaluations. But the EAG accepted that there was a high degree of inconsistency between different evaluations. It suggested that the costs used for best supportive care taken from Färkkilä et al. (2015) were not appropriate. This was because these costs related to palliative care when all active treatment options had 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 postprogression 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. Once immunotherapy is finished, people 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 scanning frequency 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. In response to the draft guidance consultation, the company agreed with the EAG's approach for resource use and applying costs for subsequent treatments using a payoff approach. So, it amended its base-case analysis.

The committee considered the appropriateness of the implementation of resource use and costs in the model. It concluded that neither the EAG's nor company's resource use exactly reflected clinical practice. But it thought that the EAG's assumptions more closely reflected the resource use and costs that would be relevant to the NHS. So, it preferred to use the implementation of resource use and costs used in the EAG's and updated company's base case.

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 it may also consider whether 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 the lack of overall-survival data included in the model (see section 3.7), and
  - the differences in projected and observed overall-survival data (see section 3.10)
- the FPNMA because:
  - it was limited to a locally confirmed dMMR or MSI-H population, and
  - a treatment class effect was assumed between the chemotherapy arms (see section 3.8)
- the point at which a long-term relative treatment effect difference should be assumed to be equal (see section 3.11).

The clinical experts explained that clinical experience of treating dMMR or MSI-H metastatic colorectal cancer suggests that unresectable disease could become resectable in up to one-third of people 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). It was noted that clinical perspectives on treating unresectable colorectal cancer are changing rapidly. So, these benefits may not have been reflected in the clinical trial outcomes. 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:

- using nivolumab-alone time to progression as a proxy for pembrolizumab time to progression (see section 3.11)

- applying the hazard ratio from the nivolumab plus ipilimumab time-to-progression curve (see section 3.11)
- applying treatment effect to the first 8 years of the model and, after this, making the hazards equal for pembrolizumab and nivolumab plus ipilimumab (see section 3.12)
- deriving time on treatment for pembrolizumab using nivolumab-alone TTD data from all treatment lines from CheckMate 8HW (see section 3.13)
- using data from the Cancer Drugs Fund clinical lead on subsequent treatment use after chemotherapy in the NHS to inform the subsequent treatments used in the model (see section 3.14)
- taking postprogression survival for people after first-line chemotherapy from the exponential fit to cohort 2 of CheckMate 142 (nivolumab plus ipilimumab), KEYNOTE 164 (pembrolizumab) and CRYSTAL (chemotherapy), weighted by proportion having each therapy (see section 3.15)
- taking time on subsequent treatment after chemotherapy from mean TTD for first-line treatment in the model for each treatment (see section 3.16)
- using 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:

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

When taking into account all of the committee's preferred assumptions, and using the committees preferred method of incremental analysis with chemotherapy and pembrolizumab, the ICER for nivolumab plus ipilimumab compared with pembrolizumab and chemotherapy was below 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.

Equality

3.20 The committee did not identify any equality issues.

Conclusion

3.21 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 below its preferred ICER threshold. So, nivolumab plus ipilimumab is recommended.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local

authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated unresectable or colorectal cancer with high microsatellite instability or mismatch repair deficiency, and the healthcare professional responsible for their care thinks that nivolumab plus ipilimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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 adviser

Jeremy Powell

Project manager

Emily Crowe

Associate director

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