NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma

1 Recommendations

1.1 Nivolumab plus ipilimumab is recommended as an option for untreated unresectable malignant pleural mesothelioma in adults, only if:

- they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- the company provides it according to the commercial arrangement (see section 2).

Why the committee made these recommendations

Standard care for untreated unresectable malignant pleural mesothelioma is chemotherapy.

The clinical trial evidence was in people with an ECOG performance status of 0 or 1. It suggests that nivolumab plus ipilimumab is likely to extend how long people live compared with chemotherapy.

Nivolumab plus ipilimumab likely meets NICE's criteria for being a life-extending treatment at the end of life. Taking this into account, the cost-effectiveness estimates for nivolumab plus ipilimumab were within the range that NICE normally considers an acceptable use of NHS resources. So it is recommended.

Issue date: December 2021

2 Information about nivolumab with ipilimumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol Myers Squibb) plus ipilimumab (Yervoy, Bristol Myers Squibb) has a marketing authorisation 'for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma'.

Dosage in the marketing authorisation

2.2 Nivolumab and ipilimumab are administered intravenously. The recommended dose is 360 mg over 30 minutes every 3 weeks for nivolumab and 1 mg per kilogram over 30 minutes every 6 weeks for ipilimumab. Treatment continues for up to 24 months or until the disease progresses. More details are available in nivolumab's summary of product characteristics.

Price

2.3 The list price of nivolumab is £2,633 per 240-mg, 24-ml vial (excluding VAT; BNF online, accessed June 2022). The list price of ipilimumab is £15,000 per 200-mg, 40-ml vial (excluding VAT; BNF online, accessed June 2022). The company has separate commercial arrangements for nivolumab and ipilimumab (simple discount patient access schemes). These make nivolumab and ipilimumab available to the NHS with discounts. The sizes of the discounts are commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discounts.

3 Committee discussion

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

The condition

Malignant pleural mesothelioma has a poor prognosis and there is an unmet need for new treatment options

3.1 Malignant pleural mesothelioma is an aggressive cancer of the pleura, the mesothelial cells surrounding the lungs. Most cases are linked to occupational exposure to asbestos, and it typically presents 20 to 50 years after exposure. The UK banned asbestos in 1999, and is now experiencing what is considered to be a peak in cases of mesothelioma. Consultation comments noted that although mesothelioma was once a disease of men in industry, it is also now being seen in women and younger people. Symptoms include breathlessness, chest pain, fatigue, lethargy, weight loss and cough. Malignant pleural mesothelioma progresses quickly and has a poor prognosis, with 8% to 10% of patients alive after 3 years according to the UK National Mesothelioma Audit in 2020 and the National Cancer Analysis System registry. A clinical expert noted that people with the condition often have comorbidities, which may also affect survival. The most common histology is epithelioid; tumours with non-epithelioid histology, which includes sarcomatoid and combined sarcomatoid–epithelioid, are less common but more aggressive, and more poorly differentiated, than epithelioid tumours. Tumours with non-epithelioid histology are associated with higher symptom burden and poorer prognosis, and respond less well to current treatment options than tumours with epithelioid histology. The expression of PD-L1 varies in malignant pleural mesothelioma. Current treatment of mesothelioma is platinum-doublet chemotherapy using pemetrexed with either cisplatin or carboplatin. A patient expert noted that immunotherapies such as nivolumab and ipilimumab offer hope for people with malignant pleural mesothelioma. The committee concluded that malignant pleural mesothelioma is an aggressive disease with a poor prognosis and there is an unmet need for new treatment options.

Tumour subtype testing

Histological testing is routine in NHS practice

3.2 The NHS tests for histological subtype of mesothelioma, but not for PD-L1 status. The testing and scoring methods for PD-L1 are not standardised in malignant pleural mesothelioma and threshold cut offs vary. There is also uncertainty about whether PD-L1 expression is associated with disease prognosis. The Cancer Drugs Fund clinical lead stated that histological testing is routine and relatively straightforward. A clinical expert stated that occasionally tissue sampling can make histological subtyping difficult. The committee concluded that histological testing of mesothelioma is standard practice in the NHS but determining PD-L1 status is not.

The company's positioning of nivolumab plus ipilimumab

Chemotherapy is the only relevant comparator for nivolumab plus ipilimumab as a first-line treatment option

3.3 The company proposes that nivolumab plus ipilimumab would offer an alternative to the standard first-line care of platinum-doublet chemotherapy using pemetrexed with either cisplatin or carboplatin. The patient experts noted that chemotherapy is associated with adverse events including nausea, vomiting, a sore mouth and alopecia. Some people may not be eligible for chemotherapy if they are frail or unable to travel for treatments, which would also apply to treatment with nivolumab plus ipilimumab. The company's pivotal trial (see section 3.4) included only people with an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, so the company does not consider best supportive care a relevant comparator. A clinical expert noted that chemotherapy is not suitable for some people, or some may choose not to have chemotherapy. For these people, best supportive care and active symptom control are standard care. However, these people would be unlikely to be offered nivolumab plus ipilimumab. The clinical expert and the Cancer Drugs Fund clinical lead both considered that excluding best supportive care as

a comparator was appropriate. The clinical expert noted that only 5% to 10% of people with the condition do not have chemotherapy. Raltitrexed was listed in the NICE scope, but the company excluded it as a comparator, arguing that it is not used in the UK. The clinical experts and the Cancer Drugs Fund clinical lead confirmed this. The committee concluded that the company's positioning of nivolumab plus ipilimumab as first-line treatment as an alternative to chemotherapy, the only relevant comparator, was appropriate.

Clinical evidence

The company provided 2 interim data cuts for the Checkmate 743 trial

3.4 The pivotal trial, CheckMate 743, is an ongoing, phase 3, randomised controlled, open-label multicentre trial (n=605). The primary end point was overall survival. The company presented the committee with 2 interim data cuts. The first was an interim analysis planned at around 403 events (419 actual); this had a median follow up of 29.7 months and a minimum of 22.1 months (referred to as the '2-year data'). After the committee's first meeting, the company provided a second analysis that was not included in the protocol; this had a median follow up of 43 months and a minimum of 35.5 months (referred to as the '3-year data'). The company considered the number of deaths at the 3-year follow up to be confidential so it cannot be reported here. The committee noted that this number was close to 473, which was the target number of events in the statistical analysis plan. The trial is ongoing and event driven; the company stated that although it had planned to stop the trial after at least 473 deaths, the trial will run until April 2023 so that the company can perform an analysis of 5-year overall survival.

The CheckMate 743 trial population is generalisable to people in UK clinical practice with ECOG scores of 0 or 1

3.5 Histological subtype was a stratification factor for randomisation in CheckMate 743, but the company stated that histological subtype was not

a planned subgroup analysis. The trial enrolled adults with histologically confirmed epithelioid or non-epithelioid disease, and with an ECOG performance status of 0 or 1. It compared the treatment effect of nivolumab 3 mg per kg every 2 weeks plus ipilimumab 1 mg per kg every 6 weeks (n=303) with pemetrexed every 3 weeks, with the investigator's choice of adding either cisplatin or carboplatin to pemetrexed (n=302). Both treatments would stop if disease progressed, if there was unacceptable toxicity, after 2 years of treatment for nivolumab plus ipilimumab, or after 6 cycles of chemotherapy. The clinical experts considered that the trial population represented patients seen in the NHS, and that if recommended, nivolumab and ipilimumab would be offered only to people with an ECOG status of 0 or 1. The committee concluded that the trial population was generalisable to patients in UK clinical practice with an ECOG score of 0 or 1.

The licensed fixed dose and weight-based dosing of nivolumab from the trial are likely to have similar efficacy

3.6 The ERG noted that the trial used body weight-based dosing of nivolumab (see section 3.4), but that the company's model used fixed dosing (360 mg every 3 weeks) to align with nivolumab's marketing authorisation. The ERG considered the effectiveness and safety of fixed dosing to be unproven because the trial provided no evidence for fixed dosing. The patient expert noted that fixed dosing requires fewer visits to hospitals and is more convenient. The clinical experts and the Cancer Drugs Fund clinical lead noted that the efficacy of fixed and weight-based dosing is similar, and explained that fixed dosing is standard practice. The committee concluded that the trial's weight-based dosing for nivolumab and the licensed fixed dose are likely to have similar efficacy, and that it is appropriate to use fixed dosing in the economic model and any recommendations.

The comparator used in Checkmate 743 reflects UK clinical practice for people with ECOG scores of 0 or 1

3.7 The committee understood that for people with ECOG performance status scores of 0 or 1, chemotherapy is the only relevant comparator (see section 3.3). The comparator in CheckMate 743 was pemetrexed plus either cisplatin or carboplatin based on investigator's choice. Among the people randomised to chemotherapy (n=302), about 66% had carboplatin and 34% had cisplatin. The ERG expressed concerns that the proportion of carboplatin compared with cisplatin used in the trial did not reflect the NICE scope and may not be generalisable to UK clinical practice. The NICE scope specified using pemetrexed with cisplatin, or carboplatin when cisplatin is unsuitable. The company provided evidence from different sources explaining that carboplatin is more widely used with pemetrexed and therefore the results in the trial represented UK practice. For example, the UK National Mesothelioma Audit in 2020, an audit of people diagnosed with mesothelioma between 2016 and 2018, reported carboplatin use in 48% of people compared with cisplatin in 20% of people with malignant pleural mesothelioma. The company considered the proportions of carboplatin and cisplatin from other sources to be confidential, so they cannot be reported here. The ERG noted that the proportions of carboplatin and cisplatin from the trial were different to those from the sources provided. The clinical experts noted that the choice between carboplatin and cisplatin is pragmatic; for example, carboplatin can be given over a shorter period of time, is less toxic, and is less expensive. The committee noted that using a 'blended comparator' could mask a clinically and cost-ineffective treatment. However, the clinical experts noted that adding carboplatin or cisplatin to pemetrexed has a similar treatment effect, and the Cancer Drugs Fund clinical lead noted that pemetrexed rather than carboplatin or cisplatin comprises the bulk of the cost of treatment. The committee concluded that proportions of cisplatin and carboplatin in the chemotherapy treatment arm in CheckMate 743 reflected UK clinical practice. It further concluded that any

recommendation would be limited to people who were candidates for chemotherapy, that is, people with an ECOG score of 0 or 1.

Clinical effectiveness

Nivolumab plus ipilimumab improves overall survival compared with chemotherapy, but its long-term treatment effect is uncertain

3.8 The primary outcome of CheckMate 743 was overall survival. The sample size was set at 606 with a targeted power of 90% and an alpha of 0.05 (2-sided) to detect a difference in mortality between the 2 treatments when 473 deaths occurred (see section 3.4) of a targeted hazard ratio (HR) 0.72. At the 2-year data cut, with a median follow up of 29.7 months, 419 deaths had occurred (89% of 473 planned for statistical analysis); 98% of people taking nivolumab plus ipilimumab and all people on chemotherapy had stopped treatment. At the 3-year data cut, the median follow up was 43 months after people had stopped treatment for at least 1 year (see section 3.4). The company considered the number of deaths at 3-year follow up to be confidential, but explained that 23% (70 of 303) of people who had treatment with nivolumab plus ipilimumab and 15% (45 of 302) who had treatment with chemotherapy were alive (numerators estimated from percentages). Results from both the interim and post hoc analyses showed that median overall survival was 18.1 months for nivolumab plus ipilimumab and 14.1 months for chemotherapy. Nivolumab plus ipilimumab was associated with longer overall survival than chemotherapy at both the 2-year (HR 0.74, 95% confidence interval [CI] 0.60 to 0.91) and 3-year follow up (HR 0.73, 95% CI 0.61 to 0.87). The company explained that the data suggested the treatment effect of nivolumab plus ipilimumab was largely maintained at 3-year follow up, and the ERG agreed. The committee noted that overall survival with chemotherapy was around 20% at 3 years on the Kaplan–Meier curve of the trial data. This was much higher than the 8% to 10% survival at 3 years from the UK registry and UK audit data provided by the company (see section 3.1). The Cancer Drugs Fund clinical lead noted that the

epidemiological data sources, for example the Cancer Analysis System, were from as far back as 2013. He noted that mesothelioma management has evolved, so survival rates have likely improved, which could explain the difference between the overall survival results for chemotherapy in the trial and the registry and audit data. A consultation comment suggested that the lower survival in the registry may be because the registry includes people with worse performance status (ECOG performance status of 2 or 3). The ERG noted that there was little change to the hazard ratio at the 3-year data cut, but that there was still uncertainty because people are alive beyond the observed period. The committee noted the sustained benefit from the 2- and 3-year data cuts and the relatively short follow up of the trial. It concluded that nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but there is uncertainty about its long-term treatment effect.

Nivolumab plus ipilimumab might improve progression-free survival but the evidence is uncertain

3.9 Progression-free survival was a secondary outcome in CheckMate 743. Disease progression was determined by blinded independent central review. Results from the 2- and 3-year data cuts showed median progression-free survival was 6.8 months for nivolumab plus ipilimumab and 7.2 months for chemotherapy. Both data cuts showed no difference between the 2 treatments according to hazard ratio estimates, but benefits started to appear at the 3-year data cut: at the 2-year data cut, the hazard ratio was 1.00 (95% CI 0.82 to 1.21; median follow up 29.7 months), but at the 3-year data cut the hazard ratio was 0.92 (95% CI 0.76 to 1.11; median follow up 43 months). The ERG also noted that 14% of people whose cancer was treated with nivolumab plus ipilimumab and 1% whose cancer was treated with chemotherapy remained progression free at 3 years. During its first meeting, the committee questioned the clinical relevance of progression-free survival in mesothelioma and its use in modelling because of the lack of evidence on nivolumab plus ipilimumab's

treatment effect on this outcome at the 2-year data cut. It also noted that the Kaplan–Meier curves by treatment allocation crossed, and although the company analysed the results in the model assuming non-proportional hazards (see section 3.17), the hazard ratio estimated from the trial assumed proportional hazards and was of limited value. The company explained that progression-free survival determined radiographically is not a reliable end point in mesothelioma because tumours may not have demarcated margins. It noted that the initial response to chemotherapy may reflect an 'early but transient' effect compared with a 'delayed but durable' effect of immunotherapy. It further explained that the progression-free survival benefit of nivolumab plus ipilimumab will only show in longer-term data. It noted that this was starting to show in the 3-year data, with 28% of people whose disease responded to nivolumab plus ipilimumab still 'in response' compared with no one who had treatment with chemotherapy. The company also explained at the second meeting that it is useful to measure progression-free survival because it can provide an element of quality of life. The committee understood that there might be some delayed but durable response to the treatment in the longer term, which may benefit survival. However, because of the non-proportional hazards as suggested by the Kaplan–Meier curves of the trial, the committee considered that the hazard ratios over time implied by the company's selected parametric distributions in modelling should be explored (see section 3.17). The committee concluded that the evidence from CheckMate 743 showed that nivolumab plus ipilimumab may improve progression-free survival compared with chemotherapy, but there is some uncertainty in the evidence.

The effect of nivolumab plus ipilimumab compared with chemotherapy is modified by histological subtype

3.10 The company presented evidence on the treatment effect of nivolumab plus ipilimumab compared with chemotherapy by histological subtype and by PD-L1 status. Results from the 2- and 3-year data cuts showed that nivolumab plus ipilimumab lowered mortality in the non-epithelioid group

(median overall survival 18.1 months) compared with chemotherapy (median overall survival 8.8 months): HR 0.46, 95% CI 0.31 to 0.68 at the 2-year data cut and HR 0.48, 95% CI 0.34 to 0.69 at the 3-year data cut. For epithelioid disease, median overall survival reduced slightly from 18.7 months at the 2-year data cut to 18.2 months at the 3-year data cut in the nivolumab plus ipilimumab arm. It increased slightly from 16.5 months to 16.7 months in the chemotherapy arm: HR 0.86, 95% CI 0.69 to 1.08 at the 2-year data cut and 0.85, 95% CI 0.69 to 1.04 at the 3-year data cut. During its first meeting, the committee noted that the treatment effect of nivolumab plus ipilimumab may be modified by histology subtype. It therefore asked the company to provide the results of a statistical analysis testing the interaction between treatment effect and histology subtype. The company provided these results during consultation, which suggested a highly significant interaction between treatment effect and histological subtype. The company noted that the trial was not powered for subgroup analyses and that these analyses were descriptive in nature. The committee, however, noted that in a small sample size, a false negative interaction test is more of a concern than a false positive. The committee noted that the Kaplan–Meier curves for epithelioid and non-epithelioid disease were similar for nivolumab plus ipilimumab (median overall survival 18.1 and 18.2 months, respectively, at 3 years), but that non-epithelioid tumours responded less well to chemotherapy. However, the committee recalled its remit to compare treatments with standard care. The committee concluded that the effect of nivolumab plus ipilimumab compared with chemotherapy is likely modified by histological subtype. The committee was also aware of its remit to appraise the technology across its indication-specific marketing authorisation and took this into account during its decision making.

PD-L1 status is not tested routinely in the NHS, so is not considered in decision making

3.11 Evidence from CheckMate 743 also showed a possible effect of PD-L1 status on mortality at the 2-year data cut, based on positive PD-L1

tumours (using a threshold of 1% or greater) or negative PD-L1 tumours, for nivolumab plus ipilimumab compared with chemotherapy. Because testing of PD-L1 in mesothelioma is not routine in the NHS (section 3.2), the committee concluded that it was not appropriate to consider it when making recommendations.

Nivolumab plus ipilimumab may improve quality of life

3.12 CheckMate 743 measured patient quality of life using the 3-level EQ-5D (EQ-5D-3L) instrument. In England, EQ-5D utility index scores range from -0.594 to 1, with higher scores indicating better quality of life. The company considered a change of 0.08 in the score of EQ-5D-3L utility index from baseline to be 'clinically meaningful' in malignant pleural mesothelioma. The company based this estimate on a randomised controlled trial (Sarna et al. 2008). This trial assessed the impact on the quality of life of people with advanced non-small-cell lung cancer of adding amifostine to radiation therapy plus chemotherapy compared with not adding it. Results from CheckMate 743 suggested that, at the 2-year data cut, the mean score of the EQ-5D-3L utility index increased over time in the nivolumab plus ipilimumab arm, from 0.70 (standard deviation [SD] 0.27) at baseline to 0.84 (SD 0.20) at week 72. In the chemotherapy arm, it remained relatively stable from baseline (mean 0.71 [SD 0.27]) but started deteriorating from week 30 (mean 0.70 [SD 0.20]), and the trend of deterioration continued onwards. The ERG noted that the trends suggested stability or improvement in quality of life for nivolumab plus ipilimumab and deterioration for chemotherapy. The committee acknowledged the trend for quality-of-life improvement for nivolumab plus ipilimumab, but noted that the company did not report group difference in EQ-5D-3L utility scores from baseline at the 2-year data cut. Also, it was not clear how the clinically meaningful change of 0.08 was defined because it was based on a single study and was in people with advanced non-small-cell lung cancer. Considering the evidence, the committee concluded that nivolumab plus ipilimumab may improve quality of life compared with chemotherapy.

Adverse events

The safety profile of nivolumab plus ipilimumab is acceptable

3.13 Evidence on adverse events was from the 2-year data cut of CheckMate 743.The company did not present additional data at the trial's 3-year data cut. The results showed that, at the 2-year data cut, more people (55%; 164 out of 300) on nivolumab plus ipilimumab experienced severe treatment-related adverse events than those on chemotherapy (25%; 72 out of 284; p value not reported). Stopping because of drug toxicity was more frequent in the nivolumab plus ipilimumab arm (23%; 69 out of 300) compared with the chemotherapy arm (16%; 45 out of 284; p value not reported). The most common adverse events with nivolumab plus ipilimumab were diarrhoea and pruritis. Respiratory tract infections were more common with chemotherapy. The company noted that most treatment-related adverse events and immune-mediated adverse events had resolved at the time of the database lock, but that endocrine-related events had not. The ERG noted that 3 people died from drug toxicity after having nivolumab plus ipilimumab because of pneumonitis, encephalitis and heart failure, compared with 1 person who had treatment with chemotherapy because of myelosuppression. The committee concluded that the safety profile of nivolumab plus ipilimumab was acceptable.

Second-line treatments

Second-line treatments used in Checkmate 743 do not reflect UK clinical practice

3.14 For the 3-year data cut, the company provided only the percentages rather than the numbers of people who had second-line treatments, and could not provide these numbers during the committee meeting. The data suggested that, at 3-year follow up, 45% (137 out of 303) of people randomised to nivolumab plus ipilimumab and 42% (128 out of 302) of people randomised to chemotherapy had second-line treatments after disease progression (numerators estimated from percentages). From the

same data cut, among the people randomised to nivolumab plus ipilimumab, about 4% (12 of 303) had immunotherapy as second-line treatment compared with 22% (65 of 302) of the people randomised to chemotherapy (numerators estimated from percentages). Also, at the 3-year data cut, about 43% (131 of 303) of the people randomised to nivolumab plus ipilimumab had chemotherapy as second-line treatment compared with 33% (100 of 302) of people randomised to chemotherapy (numerators estimated from percentages). The ERG was concerned that the second-line treatments in CheckMate 743, particularly immunotherapies, do not represent UK clinical practice. The company explained that because more people who initially had treatment with chemotherapy had immunotherapy as their second-line treatment in the trial, the trial underestimated the true treatment effect of nivolumab plus ipilimumab compared with chemotherapy (see also section 3.23). The Cancer Drugs Fund clinical lead noted that despite nivolumab having been used as second-line treatment for malignant pleural mesothelioma during the COVID-19 pandemic, it is not routinely available in the UK as a second-line treatment. The committee also noted that the NHS does not offer immunotherapy twice in practice. The company explained that the proportions of people having second-line treatments in the trial were similar to those reported in the English National Cancer Analysis System registry. This is a retrospective cohort of people with malignant pleural mesothelioma diagnosed in England between 2013 and 2017. In this registry, 44% had second-line chemotherapy, 24% had second-line vinorelbine and 19% had second-line treatment in a clinical trial. The ERG noted that these proportions were different from those in the trial, in which 16% had pemetrexed and 8% had vinorelbine as second-line treatment. The clinical experts also noted that currently there are no defined second-line treatments for the condition and their treatment effects remain unclear. The committee concluded that the second-line treatments used in CheckMate 743, particularly the immunotherapies, did not represent UK clinical practice.

Stopping rule

A 2-year stopping rule for nivolumab plus ipilimumab and a 6-cycle stopping rule for chemotherapy is appropriate

3.15 In CheckMate 743, people stopped treatment with nivolumab plus ipilimumab after 2 years if they had not already stopped treatment because of progression or unacceptable toxicity. The stopping rule did not depend on disease progression. The committee appreciated that chemotherapy was associated with a 6-cycle stopping rule to limit toxicity. The ERG noted that in Checkmate743 trial, some people had nivolumab plus ipilimumab for longer than 2 years. The ERG was concerned that if the stopping rule were not feasible in clinical practice, it may affect the clinical and cost effectiveness. After the first committee meeting, the company noted that 2 people remained on treatment beyond 24 months, because they had a delay in the final dose, but did not have additional doses. It considered the impact negligible. The committee considered this reasoning acceptable. The Cancer Drugs Fund clinical lead noted that if recommended, the NHS would only fund treatment for up to 2 years in clinical practice. The committee noted that the stopping rule for nivolumab plus ipilimumab is included in the marketing authorisation for the combined therapy. It concluded that the stopping rules for nivolumab plus ipilimumab and chemotherapy were appropriate and would be applied in clinical practice.

The economic model

The model structure is acceptable, but the extrapolations are uncertain

3.16 The company made the case that people having treatment with nivolumab plus ipilimumab accrue more quality-adjusted life years (QALYs) than people on chemotherapy. This is because they live longer, and have a higher quality of life because their disease takes longer to progress. The company used a partitioned survival model to estimate the cost effectiveness of nivolumab plus ipilimumab compared with chemotherapy.

The model included 3 health states: progression-free, progressed, and dead. The probability of being in a given health state was defined by the area under the curves for progression-free survival, overall survival, and their difference. The cycle length was 1 week and the time horizon was 20 years. The ERG noted that the company's model structure was consistent with the approach adopted in previous NICE technology appraisals in oncology, and accounted for the CheckMate 743 trial's primary (overall survival) and secondary (progression-free survival) end points. However, it was concerned that in the model, a substantial proportion of life years and progression-free life years accrued in the nivolumab plus ipilimumab arm during the extrapolated period. During its first meeting, the committee noted that this was not supported by the evidence from CheckMate 743 at the 2-year data cut and questioned the clinical relevance of progression-free survival. The committee recalled that the company noted that progression-free survival improves quality of life for people in this health state. The ERG had provided analyses showing that most of the life-year gains in the model were from the progression-free period. However, the committee noted that there was still a large proportion of life years and progression-free life years accrued from the extrapolated period when using the 3-year data. The 3-year data cut showed that the treatment effect of nivolumab plus ipilimumab was largely maintained (see sections 3.8 and 3.9), but there was no evidence on how long it would last. The committee was aware that an alternative model structure would be subject to the same uncertainties. It concluded that the company's model structure was acceptable for decision making, but that there were uncertainties in the company's extrapolations.

Modelling survival

The committee asked for further information on hazard ratios for overall survival over time, and treatment effect over time

3.17 The company assumed non-proportional hazards for overall survival because nivolumab plus ipilimumab and chemotherapy have different

mechanisms of action. It fitted parametric distributions to the 2 arms separately to extrapolate overall survival beyond the trial data. It also used data from the chemotherapy arm of the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) trial to validate the overall survival extrapolations for the chemotherapy arm. For the nivolumab plus ipilimumab arm, the company considered that the survival probability would be higher than that of the chemotherapy arm of the MAPS trial because of nivolumab plus ipilimumab's survival benefits over chemotherapy in CheckMate 743. MAPS is an ongoing, randomised, controlled, open-label trial comparing bevacizumab plus chemotherapy with chemotherapy alone in people with newly diagnosed pleural mesothelioma (median follow up 39 months). At baseline, 97% (433 out of 448) of people had an ECOG status of 0 or 1, and 81% (361 out of 448) of people had epithelioid disease compared with 19% (87 out of 448) with non-epithelioid disease. The committee noted that the MAPS study also included people with an ECOG status of 2, who were potentially at higher risk of death than people in CheckMate 743 (which excluded people with an ECOG status of 2). Data from the MAPS trial showed that the modelled hazard function should first increase, then decrease in the long term, and that survival on chemotherapy was 8% at 5 years and 0% at 10 years. To extrapolate treatment effects for the nivolumab plus ipilimumab arm, both the company and ERG agreed that the log-logistic distribution provided clinically plausible predictions and was the most appropriate. However, the committee noted that at the end of the modelled time period, the log-logistic distribution predicted better survival in the nivolumab plus ipilimumab arm than other distributions. The ERG also noted that the extrapolated overall survival from the log-logistic distribution was higher than the Kaplan–Meier curve from the trial. For the chemotherapy arm, the company preferred a 1-knot spline normal model when including data from the 3-year data cut. This model predicted survival at 5 years to be 5.2%, which the company considered was aligned with its clinical expert's estimate (5%). The clinical expert at the first meeting, who had also

advised the company, expected survival of about 5% at 5 years, and 2% at 10 years in chemotherapy arm. The ERG preferred a log-logistic model for both arms, noting that the hazard functions for both arms should be the same, both initially increasing followed by a long-term decreasing hazard. The committee recalled that nivolumab plus ipilimumab's treatment effect on overall survival may be maintained, but there was uncertainty in how long it will last (see section 3.8). Because the treatment might be associated with a survival benefit that was not yet seen in the data (see section 3.9), the committee asked to see the hazard ratios for overall survival over time implied by both the company and ERG's independent distributions, as well as the treatment effect over time as implied by the observed trial data.

Using a log-logistic distribution to extrapolate overall survival for both treatments may be appropriate but there are uncertainties

3.18 In response, the company plotted the hazard ratios implied by both the company and ERG's preferred extrapolations for overall survival, alongside the smoothed hazard ratio and its 95% confidence intervals based on the observed data from CheckMate 743. The figure indicated that the hazard ratios implied by the selected distributions, as well as the smoothed hazard ratio based on observed trial data, fluctuated over time but were all below 1, and the 95% confidence interval of the smoothed hazard ratio was wide. The company stated that the plotted hazard ratios over time showed sustained treatment effect and the selected distributions aligned with the smoothed hazard ratio. However, the ERG commented that neither extrapolation could be ruled out and that they may not be so informative, especially given the increasingly wide confidence interval at the end of the smoothed hazard ratio. The committee noted the implied treatment effects in the longer term were based on a small number of patients. It also noted the high uncertainty beyond 24 months, at which point the extrapolated curves started to diverge. The committee noted that there were minor differences between the company and ERG's extrapolations, and that the ERG's extrapolations indicated a smaller

treatment effect over time and were more reasonable. The committee concluded that the log-logistic distribution was appropriate for extrapolating overall survival in both arms, but that how long the treatment effect would continue in the long term was uncertain.

The company's parametric distributions for extrapolating progression-free survival are appropriate

3.19 The company fitted independent parametric distributions to model progression-free survival in the 2 treatment arms guided by the best statistical and visual fit to the Kaplan–Meier curve of CheckMate 743. The company and ERG agreed that for extrapolating progression-free survival, the generalised gamma distribution was appropriate for nivolumab plus ipilimumab and the log-logistic distribution was appropriate for chemotherapy. However, the ERG was concerned that a substantial proportion of progression-free life years accrued beyond the observed data in the model, extrapolated from either the 2- or 3-year data cuts (see section 3.16). The committee noted that, at the 3-year data cut, the evidence from CheckMate 743 appeared to show some benefit of nivolumab plus ipilimumab in the period before progression. The evidence also suggested there may be a continued response to treatment and a survival benefit (see section 3.9). Given that there was no long-term evidence, the committee also looked at the hazard ratios for progression-free survival over time implied by the extrapolation agreed between the company and ERG, as well as the treatment effect over time as implied by the observed trial data. The company provided these figures, which were all below 1, suggesting the treatment effect may be maintained. The committee noted that the hazard ratios implied by the company and the ERG's preferred distributions were largely aligned with the smoothed hazard ratio and within the bounds of its 95% confidence interval. However, it also noted the uncertainties, given the short follow up of the trial and the fact that the extrapolations were based on a small number of patients. The committee concluded that it was appropriate to use the

generalised gamma distribution to extrapolate progression-free survival for nivolumab plus ipilimumab, and use the log-logistic for chemotherapy.

It is reasonable to assume some treatment effect waning

3.20 The company's base case predicted survival for the 20-year horizon of the model based on independently fitted models for overall survival; the company did not factor waning of treatment effect into the analysis. The ERG considered that this was not reasonable in the absence of long-term clinical experience. It noted that the company based its argument on expert opinion, but it was not clear how the company chose the experts or elicited their opinion. The ERG considered it appropriate to assume that the treatment effect would wane 5 years after treatment starts and 3 years after treatment stops. It acknowledged that this duration was arbitrary, but had been accepted in other NICE technology appraisals, including nivolumab for treating recurrent or metastatic squamous cell carcinoma of the head and neck after platinum-based chemotherapy. During its first meeting, the committee also noted the evidence presented by the company in its response to clarification questions, which suggested that the treatment effect of immunotherapies is maintained for up to 4 years in non-small-cell lung cancer (Antonia et al. 2019). However, the Cancer Drugs Fund clinical lead noted that some tumours treated with immunotherapies relapsed. The committee considered that there appeared to be a continuing benefit after stopping treatment, but it was unclear how long it would last, so it would be reasonable to assume some treatment effect waning.

When nivolumab plus ipilimumab is stopped at 2 years, it is acceptable to assume an additional survival benefit for 3 more years

3.21 At the committee's second meeting, the company provided 6 scenario analyses that assumed treatment effect waning at 5, 7, or 10 years after starting treatment (with a duration of treatment effect waning of 5 or 10 years for each). All of the scenarios worsened the cost-effectiveness estimates, and the longer after starting the treatment the waning occurred,

the better the cost-effectiveness estimate. The committee recalled the uncertainties around the treatment effects over time as implied by the company and ERG's extrapolations for overall survival (see section 3.18) and progression-free survival (see section 3.19). It was also aware that most people in the CheckMate 743 trial had died by the 3-year data cut (see section 3.8). It therefore did not consider it reasonable to rule out the possibility of treatment effect waning in the model. The Cancer Drug Fund clinical lead noted that treatment effect waning 5 years after starting treatment has been accepted in previous NICE technology appraisals for immunotherapies in which there was a 2-year stopping rule. Considering this and the uncertainties in the evidence base, the committee concluded that it is acceptable to assume that if the treatment is stopped at 2 years, it is likely that its survival benefit would continue for 3 more years, and treatment waning could reasonably start at this point.

Utility values

Using treatment-dependent utility benefits up to 3 years is appropriate

3.22 The company used patient-level data on utility from CheckMate 743 to estimate the utility values for the progression-based health states in the model. The company's analysis showed that having treatment or not significantly impacted utility values. The company therefore adopted treatment-dependent health state utilities in its base case and assumed that the treatment-dependent utility benefits would last for the whole duration of the time horizon. The ERG considered that implausible. For its base case, the ERG adopted treatment-dependent utilities (with the nivolumab plus ipilimumab utility benefit) for up to 3 years, and treatment-independent utilities after this. The ERG chose 3 years because only 3 people were at risk of death at 3 years in the trial according to the evidence at the 2-year data cut that the company presented at the first committee meeting (see section 3.8). The company adopted the ERG's assumption after technical engagement. The committee agreed that using

treatment-dependent utility benefits up to 3 years and treatment-independent utilities afterwards was appropriate.

Adjusting for second-line treatments

It is appropriate to use the inverse probability censoring weights method to adjust for second-line treatments not used in the NHS

3.23 The company modelled second-line treatment based on the distribution of the second-line treatments used in CheckMate 743, but these treatments did not reflect UK clinical practice (see section 3.14). Second-line treatments used in the trial included pemetrexed, carboplatin, cisplatin, gemcitabine, vinorelbine, bevacizumab and several immunotherapies (nivolumab, ipilimumab, pembrolizumab). During its first meeting, the committee suggested that the company adjust the overall survival results and remove the costs for second-line treatments that do not reflect NHS practice and may be associated with improving survival. After consultation, the company presented analyses adjusting for second-line treatment using 4 methods: inverse probability censoring weights (IPCW), 2-stage estimation, rank preserving structural failure time model (RPSFTM), and iterative parameter estimation. The company preferred the IPCW method because it addresses informative censoring. It did not prefer the RPSFTM and iterative parameter estimation methods because they assume the same treatment effect for all patients regardless of when they have treatment, or the 2-stage estimation method because it could result in informative censoring when patients do not die during the study. The ERG did not critique the company's methods in detail but noted that the methods were appropriate and the results were similar across the different methods. Because of the lack of reporting, the committee asked to see further details of the methods considered. The company provided these details at the second committee meeting. It also removed all non-NHS second-line treatment costs from both arms. The committee's discussion on adjusting for second-line non-NHS-treatments focused on the intention-to-treatment population during its second). It noted that, for

the intention-to-treat population, the company still preferred the IPCW method for its base case. The ERG agreed that theoretically the IPCW method was preferable, but stated that all methods gave similar results. The committee concluded that the IPCW method may be appropriate for adjusting for second-line non-NHS treatments for the intention-to-treat population, but that it was based on important assumptions around there being no unmeasured confounding.

End of life

Nivolumab plus ipilimumab is likely to meet NICE's end of life criteria for the population in the marketing authorisation

3.24 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The Cancer Analysis System registry reported 13-month median survival with first-line chemotherapy. Median overall survival was 14 months with chemotherapy in CheckMate 743 for people who had an ECOG status of 0 or 1; and mean overall survival for chemotherapy estimated from the model was about 20 months. Overall survival in the chemotherapy arm in the ERG base case was up to 21 months. The committee agreed that life expectancy for people with unresectable malignant pleural mesothelioma who have standard care is likely to be less than 24 months. Results from CheckMate 743 showed a median 4-month survival benefit for nivolumab plus ipilimumab compared with chemotherapy at a median 43-month follow up. The ERG base case also supported a mean survival gain of greater than 3 months. The committee acknowledged that these survival estimations were based on the company and ERG base cases, so there was an element of uncertainty. But it concluded that nivolumab plus ipilimumab was likely to meet the end of life criteria for untreated unresectable malignant pleural mesothelioma for the population in the marketing authorisation.

Cost effectiveness

The cost-effectiveness estimates are within the range considered an acceptable use of NHS resources

3.25 The patient access schemes for the comparator treatments mean that the costs and cost-effectiveness estimates are confidential and cannot be presented. Taking into account the end of life criteria, the committee noted that the incremental cost-effectiveness ratio (ICER) that reflected its preferred assumptions was less than £50,000 per QALY gained for the intention-to-treat population. It concluded that the ICER for nivolumab plus ipilimumab for treating malignant pleural mesothelioma is within the range normally considered a cost-effective use of NHS resources.

Conclusions

Nivolumab plus ipilimumab is recommended for routine use in the NHS

3.26 The committee concluded that it could recommend nivolumab plus ipilimumab for treating malignant pleural mesothelioma.

Equality issues

There are no equality issues related to protected characteristics

3.27 The committee considered several potential equalities issues raised by stakeholders:

- The condition is a preventable occupational-related disease with a higher incidence in heavy industries. People with the condition may have lower socioeconomic status than people with other cancer types.
- People with mesothelioma are often old, and the cancer is diagnosed at a late stage when they can be too frail to travel for treatment. This may limit their treatment options.
- Some people are unable to self-fund or do not have access to funding from compensation claims.

The committee noted the prevalence of mesothelioma in certain areas of the country. It noted that people too frail to travel would be unlikely to be offered treatment (section 3.3). It was aware that the prevalence of a disease, physical access to the treatment, and socioeconomic status are not protected characteristics and are therefore not within NICE's remit when making recommendations. The technology will be available for all people regardless of age, geographical location and socioeconomic status. The committee concluded that these are not equality issues.

Guidance for pleural mesothelioma should also cover mesothelioma of the pericardium or peritoneum

3.28 The committee heard from the Cancer Drugs Fund clinical lead that, rarely, mesotheliomas can occur in the pericardium or peritoneum. They noted that any guidance for pleural mesothelioma should extend to these individuals. The committee agreed.

Innovation

Nivolumab plus ipilimumab is not innovative

3.29 NICE defines innovation as a 'step-change' in treatment with benefits not accounted for in the modelling. The company considers nivolumab plus ipilimumab innovative because it is the first-in-class immunotherapy for a condition for which there have been no new therapies in the last 2 decades. The clinical experts considered it a step-change in treatment. The committee agreed, but did not hear of any additional gains in health-related quality of life not already captured in the modelling. A clinical expert noted that the cost-effectiveness estimates may not capture the benefit of nivolumab plus ipilimumab in reducing anger about having an occupational disease, but the committee was not presented with evidence for this. The committee concluded that the technology may be a step-change in treatment, but it did not identify benefits not captured by the company's economic modelling. It therefore considered that nivolumab

plus ipilimumab is not innovative for untreated unresectable malignant pleural mesothelioma.

4 Review of guidance

4.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee
July 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

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

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

NICE project team

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

Samuel Slayen, Heather Stegenga

Technical leads

Yelan Guo

Technical adviser

Daniel Davies, Joanne Ekeledo

Project managers

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