NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma

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

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

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

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

Issue date: August 2021

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

After consultation:

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 20 September 2021

Second appraisal committee meeting: 7 October 2021

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 Nivolumab plus ipilimumab is not recommended, within its marketing authorisation, for untreated unresectable malignant pleural mesothelioma in adults.

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

Why the committee made these recommendations

Standard care for untreated unresectable malignant pleural mesothelioma is chemotherapy.

Clinical trial evidence suggests that nivolumab plus ipilimumab may extend how long people live compared with chemotherapy, but for how long is uncertain.

Whether nivolumab plus ipilimumab is cost effective is currently unknown because of uncertainties in the clinical evidence and the economic model. It likely meets NICE's criteria for being a life-extending treatment at the end of life. However, because its cost effectiveness is uncertain, it is not recommended for routine use in the NHS. Nivolumab plus ipilimumab does not meet the criteria to be considered for the Cancer Drugs Fund because it currently does not have the potential to be cost effective. Therefore, it is not recommended for use in the Cancer Drugs Fund.

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 Both 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 is continued for up to 24 months or until 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 per 24-ml vial (excluding VAT; BNF online, accessed August 2021). The list price of ipilimumab is £15,000 per 200 mg per 40-ml vial (excluding VAT; BNF online, accessed August 2021). The company has commercial arrangements for nivolumab and ipilimumab (simple discount patient access schemes). These make nivolumab and ipilimumab available to the NHS with discounts and would have also applied to this indication if the technology had been recommended. The size of the discounts is 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 [Add link to website in-development page on '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 type of cancer that occurs in the pleura – the mesothelium (membranous lining) surrounding the lungs. Most cases are linked to occupational asbestos use, and it typically presents 20 to 50 years after exposure. As asbestos was banned in the UK from 1999, the UK is now experiencing a peak in cases. 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 or combined sarcomatoid and epithelioid, are less common but more aggressive, and more poorly differentiated than epithelioid tumours. They are associated with higher symptom burden and poorer prognosis, and respond less well to current treatment options. There is variation in programmed death-ligand (PD-L1) expression in malignant pleural mesothelioma. Treatment currently available is chemotherapy, and the options are limited. A patient expert noted that this is hard for people to accept. Another patient expert noted that immunotherapies offer 'hope'. 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 clinical experts noted that they offer chemotherapy to all people fit enough to receive it, regardless of histology subtypes or PD-L1 status of

the tumour. They stated that the NHS tests for histological subtype, but not for PD-L1. The testing and scoring methods for PD-L1 are not standardised in malignant pleural mesothelioma and there is a wide variation in threshold cut offs. There is also uncertainty about whether PD-L1 expression is associated with disease prognosis. The committee heard from the Cancer Drugs Fund clinical lead that histological testing is routine and relatively straightforward. A clinical expert stated that occasionally tissue sampling can make determining the histological subtype 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, 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 committee was aware that 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 some people are not fit enough for chemotherapy or may choose not to have chemotherapy; for these people, best supportive care and active symptom control are standard care. However, the clinical expert noted that only 5% to 10% of people with the condition do not have chemotherapy. Both the clinical expert and the Cancer Drugs Fund clinical lead considered that excluding best supportive care as a comparator is appropriate. The company also excluded raltitrexed, listed in the NICE

scope as a comparator, arguing that it is not used in the UK and so is not a relevant comparator either; 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, is appropriate.

Clinical evidence

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

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, that is, the difference in time from randomisation to death between treatments. Histological subtype was a stratification factor for randomisation. 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/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (n=303) with pemetrexed every 3 weeks, with the investigator's choice of adding either cisplatin or carboplatin to it (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 expert considered that the trial population represented patients seen in the NHS. 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 from the trial have similar efficacy

3.5 The ERG noted that the trial used weight-based dosing of nivolumab (see section 3.4) but 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 uncertain because there is no evidence for fixed dosing from the trial. The patient expert noted that fixed dosing requires less frequent 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. They 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

3.6 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 infusion of pemetrexed with either cisplatin or carboplatin based on investigator's choice. Among patients randomised to chemotherapy (n=302), about 66% had carboplatin and 34% had cisplatin. The ERG expressed concerns that the proportion of carboplatin versus cisplatin used in the trial did not reflect the NICE scope and may not be generalisable to UK clinical practice. This is because the NICE scope specifies the use of pemetrexed with cisplatin, and that carboplatin may be used when cisplatin is unsuitable. The company provided evidence from different sources explaining that the results in the trial represented UK practice and that carboplatin is more widely used with pemetrexed. For example, the UK National Mesothelioma Audit in 2020, an audit of patients diagnosed with mesothelioma between 2016 and 2018, reported carboplatin use in 48% compared with cisplatin in 20% of people with malignant pleural mesothelioma. The proportions from other sources provided by the company were confidential so cannot be reported here. The ERG noted that the proportions from the trial were different to the sources provided. The clinical expert 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 expert 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 using cisplatin and carboplatin in the chemotherapy treatment in CheckMate 743 reflected UK clinical practice. The committee 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.

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

3.7 Forty four percent (134 out of 303) of patients randomised to nivolumab plus ipilimumab and 41% (123 out of 302) of patients randomised to chemotherapy had second-line treatments following disease progression in CheckMate 743. Among the patients randomised to nivolumab plus ipilimumab, about 3% (10 of 303) had immunotherapy as second-line treatment versus 20% (61 of 302) of the patients randomised to chemotherapy. About 43% (131 of 303) of the patients randomised to nivolumab plus ipilimumab had chemotherapy as second-line treatment versus 32% (95 of 302) of patients randomised to chemotherapy. The ERG expressed concerns that second-line treatments in CheckMate 743 do not represent UK clinical practice, particularly immunotherapies at second line. The company explained that, because more patients treated with chemotherapy had immunotherapy as their second-line treatment in the trial, the trial would have underestimated the true treatment effect of nivolumab plus ipilimumab. 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 because of the risk of immunosuppression, it is not routinely available in the UK as

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, a retrospective cohort of patients 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, and 24% had vinorelbine. The ERG noted that these were different from the trial where 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 noted the difficulties in separating results based on the line of treatment but noted that, while not optimal, statistical analyses adjusting for second-line treatments had not been presented. The committee concluded that the second-line treatments used in CheckMate 743, particularly the immunotherapies, did not represent UK clinical practice, and that trial results that adjusted overall survival for second-line treatments would better reflect the difference between nivolumab plus ipilimumab and chemotherapy.

Clinical effectiveness

Nivolumab plus ipilimumab improves overall survival compared with chemotherapy, but its effect may be overestimated

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 the difference between the 2 treatments. The company planned an interim analysis when 403 deaths occurred and a final analysis when 473 deaths occurred. At the interim analysis in April 2020 (median follow up time 29.7 months), 419 deaths had occurred (89% of 473 planned); 98% of patients taking nivolumab plus ipilimumab and all patients on chemotherapy had stopped treatment. Results from the

interim analysis 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 (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.60 to 0.91). The committee noted that overall survival with chemotherapy was around 20% at 3 years on the Kaplan–Meier curve of the trial data. This is much higher than the 8% to 10% survival at 3 years from 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; 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. The committee also recognised that early results from trials that report benefit are likely to overestimate the treatment effect of the drug under investigation. The committee concluded that nivolumab plus ipilimumab reduces the risk of death in people with malignant pleural mesothelioma compared with chemotherapy, but that the interim trial analysis may have overestimated the magnitude of this difference.

Nivolumab plus ipilimumab had no impact on progression-free survival

3.9 Progression-free survival was a secondary outcome in CheckMate 743. Disease progression was determined by blinded independent central review. Results from the April 2020 data cut showed median progression-free survival was 6.8 months for nivolumab plus ipilimumab and 7.2 months for chemotherapy, and there was no difference between the 2 treatments: HR 1.00, 95% CI 0.82 to 1.21, median follow up 29.7 months. The committee noted that the Kaplan–Meier curves of the trial crossed, and the company analysed the results assuming non-proportional hazards in the model (see section 3.17). The company noted 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. The company stated, without evidence, that the benefit of nivolumab plus ipilimumab on progression-free survival will only show in longer-term data. The clinical expert noted that progression-free survival was not used clinically. He further noted that while progression-free survival may be a surrogate for overall survival for chemotherapy, this is not the case for immunotherapies in oncology. The committee asked the clinical expert whether progression-free survival is used clinically, given that both nivolumab and ipilimumab are offered for a limited period. The clinical expert explained that progression does not direct treatment decisions in mesothelioma. The committee asked why the company had used progression-free survival in its model (section 3.15). The company explained that it is challenging to see nivolumab plus ipilimumab's benefit in terms of progression-free survival in mesothelioma without long-term data, and it developed the partitioned survival model after consulting clinical experts. The committee concluded that the evidence from CheckMate 743 showed that nivolumab plus ipilimumab did not improve progression-free survival compared with chemotherapy, and that this outcome may have limited clinical relevance for assessing treatment effect. The committee took account of these points in its decision-making.

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

3.10 The company presented evidence on the treatment effect of nivolumab plus ipilimumab in comparison with chemotherapy by histological subtype and by PD-L1 status. Results from the April 2020 data cut 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. For epithelioid disease, median overall survival at the April 2020 data cut was 18.7 months for nivolumab plus ipilimumab and 16.5 months for chemotherapy: HR 0.86, 95% CI 0.69 to 1.08. The company noted the trial was not powered for subgroup analyses and that the subgroup

analyses were descriptive in nature; the committee asked whether the company had done, but simply not reported, statistical tests for interaction, and the company could not answer. 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 18.7 months, respectively), but non-epithelioid tumours responded less well to chemotherapy. The committee concluded that the effect of nivolumab plus ipilimumab compared with chemotherapy appeared to be modified by histological subtype, which is assessed in the NHS. The committee was also aware of its remit to appraise the technology across its indication-specific marketing authorisation.

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 April 2020 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 the committee had heard that testing of PD-L1 for mesothelioma is not routine in the NHS (section 3.2), the committee concluded that it was not appropriate to consider it in making recommendations.

Nivolumab plus ipilimumab may be associated with improved quality of life

3.12 CheckMate 743 measured quality of life in patients using the three-level EuroQol-5 Dimension (EQ-5D-3L) instrument. 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’. The company based this estimate on a randomised controlled trial (Sarna et al. 2008) assessing the impact of adding amifostine to radiation therapy plus chemotherapy versus not adding it on the quality of life of people with advanced non-small-cell lung cancer. Results from CheckMate 743 suggested that, at

the data cut of April 2020, the mean EQ-5D-3L utility index score 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. Conversely, the mean EQ-5D-3L utility index score remained relatively stable in the chemotherapy arm and then started deteriorating from week 30, falling from 0.71 (SD 0.27) at baseline to 0.70 (SD 0.20) at week 30, 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 April 2020 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 in people with advanced non-small-cell lung cancer. Considering the evidence and on balance, the committee concluded that nivolumab plus ipilimumab may be associated with improved quality of life compared with chemotherapy.

Adverse events

The safety profile of nivolumab plus ipilimumab is acceptable

3.13 Results from CheckMate 743 showed that, at the April 2020 data cut, more patients (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, and 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 patient treated with chemotherapy from myelosuppression. The committee concluded that the safety profile of nivolumab plus ipilimumab was acceptable.

Stopping rule

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

3.14 Checkmate 743 had a 2-year stopping rule for people treated with nivolumab plus ipilimumab if they had not already stopped treatment because their condition progressed or the treatment caused unacceptable toxicity. The stopping rule did not depend on disease progression. The ERG noted that at the April 2020 data cut, a few patients had been having nivolumab plus ipilimumab for longer than 2 years. The ERG was concerned that if this stopping rule is not feasible for clinical practice, it may have clinical and cost-effectiveness impact for the modelling of the technology. The committee appreciated that the results of the trial may overestimate the treatment effect that nivolumab plus ipilimumab would have when used in the NHS. The Cancer Drugs Fund clinical lead noted that the treatment would only be funded for up to 2 years in clinical practice. The committee appreciated that chemotherapy was associated with a 6-cycle stopping rule. The committee noted that the stopping rule for nivolumab plus ipilimumab is included in the marketing authorisation for the combined therapy. It noted that stopping rules for both nivolumab plus ipilimumab and chemotherapy are appropriate and would be applied in clinical practice, but that protocol violations related to the 2-year stopping rule in the trial means that the results may overestimate the treatment effect of nivolumab plus ipilimumab.

The economic model

The model structure is acceptable, but the extrapolations are uncertain

3.15 The company made the case that people treated with nivolumab plus ipilimumab accrue more quality-adjusted life years than people on chemotherapy 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 is 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 end point (progression-free survival). 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. The ERG considered that the company should develop a state transition model to verify the extrapolations from the partitioned survival model and address the uncertainties. The company argued that state transition models are not recommended over partitioned survival models, that one would not necessarily result in different results, and that it would not be reasonable for the company to develop both models. The committee understood that partitioned survival models are common and standard for modelling in oncology. It noted that the substantial proportion of life years and progression-free life years accrued beyond the observed data were not supported by the evidence from CheckMate 743 at the April 2020 data cut (see sections 3.8 and 3.9). The committee recalled that progression-free survival was perhaps not a clinically relevant end point for immunotherapies for treating cancers, that

progression-free survival and overall survival did not necessarily correlate in immunotherapies, and that there is a lack of long-term data (see section 3.9). The ERG also noted that it preferred to externally validate extrapolations with data. The committee was aware that an alternative model would be subject to the same uncertainties. It concluded that the company's model structure was acceptable for decision-making but there were uncertainties in its extrapolations.

Modelling survival

Using a log-logistic distribution to extrapolate overall survival for both treatments is appropriate

3.16 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 patients had an ECOG status of 0 or 1, and 81% (361 out of 448) of patients had epithelioid disease versus 19% (87 out of 448) with non-epithelioid disease. The company could not tell the committee how the MAPS population compared to that of CheckMate 743. 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. The committee agreed that the log-logistic distribution was appropriate for the extrapolation of overall survival in the nivolumab plus ipilimumab arm. For the chemotherapy arm, the company preferred a 2-knot spline model. This model predicted survival at 5 years to be 3.6%, which it considered aligned with the estimate of the company's clinical expert (5%). The clinical expert at meeting, who had also advised the company, expected survival of about 5% at 5 years, and 2% at 10 years. The ERG noted that spline models could provide good within-trial fits, but did not necessarily improve extrapolation. The committee considered that the log-logistic model provided a better visual fit than the 2-knot spline model. The ERG preferred the log-logistic distribution for the chemotherapy arm because its predicted overall survival at 5 years was 7.5%, which was still lower than but was more in line with the 8% reported for chemotherapy in the MAPS trial at this time point. The committee concluded that the log-logistic distribution was appropriate to extrapolate overall survival for both treatments.

The extrapolated progression-free survival is uncertain

3.17 The company fitted independent parametric distributions to model progression-free survival in the 2 treatment arms. The fitting was guided by the best statistical and visual fit to the Kaplan–Meier data of CheckMate 743. The company did not consider MAPS data appropriate for validating the extrapolation of progression-free survival in the nivolumab plus ipilimumab arm because of the low proportion of patients with progression-free survival at the end of both trials. During clarification, the company stated that the extrapolated progression-free survival for chemotherapy was in line with MAPS trial data up to 5 years. The company and ERG agreed that the generalised gamma distribution was appropriate for extrapolating progression-free survival for nivolumab plus ipilimumab and the log-logistic distribution was appropriate for

chemotherapy. However, the ERG was concerned that in the model, a substantial proportion of progression-free life years accrued beyond observed data. The ERG performed 2 scenario analyses (using either log-logistic or generalised gamma for both treatments); both increased the cost-effectiveness estimates. It noted that longer-term data would help reduce the uncertainties. The committee also questioned the plausibility of the large proportion of life years being accrued after the disease had progressed in the model. The clinical expert explained that some benefit after progression is plausible. The committee was aware that the evidence from CheckMate 743 did not support the benefit of nivolumab plus ipilimumab in progression-free survival (see section 3.9) in terms of time spent before progression in the model. It also recalled that progression-free survival may have little clinical relevance (see section 3.9). The company justified using a health state for progression-free disease, noting that it was traditional for cancer therapies. Given these points, the committee considered that there was a high level of uncertainty related to the plausibility of progression-free survival's extrapolation, and it would take this into account during decision-making.

Continued treatment benefit up to 5 years is acceptable

3.18 The company assumed in its base case that the relative treatment effect would be maintained over the 20-year horizon of the model (that is, there would be no waning of treatment effect). The ERG considered that this assumption 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 expert or elicited the expert's opinion. The ERG considered it appropriate for the treatment effect to wane 5 years after treatment started; it acknowledged that this duration is arbitrary, but had been accepted in appraisals in head and neck cancer. The ERG also considered that a later data cut may help. The committee did not accept unremitted perpetual benefit after treatment stops, but also considered that one could not generalise from one cancer to another, particularly given the probable effect modification by histology

(section 3.10). In the absence of evidence and considering these factors, the committee concluded that waning after 5 years was acceptable.

Utility values

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

3.19 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 patients were at risk at 3 years in the trial. 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.

Second-line treatment costs

The company's modelling of second-line treatments may underestimate the cost-effectiveness estimate for nivolumab plus ipilimumab

3.20 The company modelled second-line treatment based on the distribution of the second-line treatments used in CheckMate 743 (see section 3.7). It applied a treatment duration of 1.7 months for all second-line treatments in the model. These included pemetrexed, carboplatin, cisplatin, gemcitabine, vinorelbine, bevacizumab and several immunotherapies (nivolumab, ipilimumab, pembrolizumab). The company did not estimate duration from the trial. Instead, it obtained the estimate of 1.7 months from Waterhouse et al. (2019), a retrospective observational study on

treatment patterns and outcomes in people with advanced mesothelioma starting systemic therapy between January 2008 and December 2016 in the US (n=474). The ERG noted that there was a large variation in the duration of second-line treatments in the Waterhouse 2019 study (interquartile range: 1 to 11.9 months). The ERG considered that assuming equal treatment duration for all second-line treatments was not plausible. The experts noted that there are no defined second-line treatments and their effects are not clear. Nonetheless, a clinical expert noted during the technical engagement that 1.7 months was not long enough; they considered that it should be at least 4 months for pemetrexed and vinorelbine. The company considered that CheckMate 743 would favour the treatment effect of chemotherapy because more people in the chemotherapy arm had immunotherapy as their second-line treatment in the trial (see section 3.7). But the clinical expert explained that it is not clear if immunotherapies are effective as second-line treatments. The ERG could not vary the duration of second-line treatment by therapy in the model but applied a 3-month treatment duration to all second-line treatments in a scenario analysis, noting a small increase in the cost-effectiveness estimate. The committee understood that the second-line treatments in CheckMate 743 did not reflect UK clinical practice (see section 3.7). It noted that the company did not adjust the overall survival hazard ratios for second-line treatments. The committee also considered that if the costs of the second-line treatments were removed from the model, it would probably worsen the estimates of nivolumab plus ipilimumab's cost-effectiveness. The committee concluded that the company's modelling of second-line treatments may have led to the cost-effectiveness estimate of nivolumab plus ipilimumab compared with chemotherapy being underestimated.

End of life

Nivolumab plus ipilimumab is likely to meet the end of life criteria

3.21 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. Life expectancy for people with malignant pleural mesothelioma is shorter than 24 months. 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 ERG base case was up to 24 months. The committee agreed that life expectancy for people with unresectable malignant pleural mesothelioma who receive standard care is likely to be less than 24 months, but noted that there may be differences in life expectancies by histological subgroup (see section 3.10). Results from CheckMate 743 showed a median 4-month survival benefit for nivolumab plus ipilimumab compared with chemotherapy at a median 29.7-month follow up. The ERG base case also supported a mean survival gain of greater than 3 months. The committee noted that nivolumab plus ipilimumab was likely to give a mean extension to life of at least 3 months for people with untreated malignant pleural mesothelioma, but that this might differ by histological subtypes. It concluded that nivolumab plus ipilimumab was likely to meet the end of life criteria for untreated unresectable malignant pleural mesothelioma.

Cost effectiveness

There are uncertainties in the evidence and in the company's modelling assumptions

3.22 The committee noted uncertainty in the evidence and the company's modelling assumptions. Specifically:

- Second-line treatments used in Checkmate 743 do not reflect UK practice (see section 3.7).
- Nivolumab plus ipilimumab improves overall survival, but the magnitude of the effect over the long term is unproven (see section 3.8).
- There are potential biases in the magnitude of the benefit associated with nivolumab plus ipilimumab for overall survival because the company presented interim analyses and a proportion of trial participants did not stop treatment at 2 years (see section 3.14).
- Nivolumab plus ipilimumab's benefit in terms of progression-free survival was not shown in Checkmate 743, and the relevance of this end point for assessing nivolumab plus ipilimumab's treatment effect on mesothelioma is uncertain (see section 3.9).
- A substantial proportion of life years and progression-free life years accrued beyond observed data in the model (see section 3.15).
- The company's modelling of second-line treatments may have biased the cost-effectiveness estimate for nivolumab plus ipilimumab treatment (see section 3.20).

There are preferred assumptions for the analyses

3.23 The committee would prefer analyses using the following assumptions:

- Using a log-logistic distribution to extrapolate overall survival for both arms (see section 3.16).
- A 2-year stopping rule (see section 3.14).
- Assuming no treatment benefit for nivolumab 5 years after the treatment starts (see section 3.18).

- Treatment-dependent utility benefits for up to 3 years and then treatment-independent utility afterwards (see section 3.19).
- Using a generalised gamma distribution to extrapolate progression-free survival for nivolumab plus ipilimumab and a log-logistic distribution for chemotherapy (see section 3.9).
- Limiting the proposed population to people with an ECOG performance status of 0 or 1 (see section 3.3).

Further evidence and analyses are needed

3.24 The committee would prefer to see evidence and analyses that address the following:

- Nivolumab plus ipilimumab's long-term effect on overall survival (see section 3.8).
- Nivolumab plus ipilimumab's long-term treatment effect on progression-free survival and whether this end point is clinically relevant for the assessment.
- The uncertainty in the extrapolation of progression-free survival in the model (see sections 3.9 and 3.17).
- Adjusting for overall survival and costs for second-line treatments that do not reflect NHS clinical practice (see sections 3.7 and 3.20).
- Whether nivolumab plus ipilimumab's treatment effect interacts with histological subtypes in mesothelioma (see section 3.10).
- The uncertainty about whether the end of life criteria are met for all potentially relevant subgroups (see section 3.21).

The true incremental cost-effectiveness estimate is unknown

3.25 The committee considered that the true incremental cost-effectiveness estimate was unknown given the uncertainties in the evidence and modelling.

Nivolumab plus ipilimumab is not recommended for routine use in the NHS

3.26 The committee noted that even in the company's own base case, the estimates of cost effectiveness were far higher than what NICE considers to be good value for money. The committee noted that the ERG's estimates were even higher. It recognised that the most plausible cost-effectiveness estimate was currently unknown. It concluded that it could not recommend nivolumab plus ipilimumab for malignant pleural mesothelioma across its marketing authorisation. Having determined this, the committee sought to optimise treatment in an identifiable subgroup. However, the committee had not been presented with cost-effectiveness analyses or end of life evidence by histological subgroup. The committee wished to make guidance to include as many people as possible, and the estimates of cost effectiveness across the marketing authorisation were sensitive to the current price. It concluded that it could not recommend nivolumab plus ipilimumab for malignant pleural mesothelioma for routine use in the NHS.

Nivolumab plus ipilimumab is not recommended for use in the Cancer Drugs Fund

3.27 The committee then considered if nivolumab plus ipilimumab could be recommended within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee noted that:

- The company expressed an interest in the treatment being considered for funding through the Cancer Drugs Fund;
- The CheckMate 743 trial is ongoing and due to complete in April 2023;

- Data from the trial may help explore the uncertainties in the treatment effect of nivolumab plus ipilimumab over a longer term;
- To enter the Cancer Drugs Fund, the treatment must have 'plausible potential' to be cost effective.

The committee recalled that the true incremental cost-effectiveness estimate is unknown (see section 3.25) but recognised that, at the price the company had chosen to charge, nivolumab plus ipilimumab is not plausibly cost effective, even in the company's own modelling. The committee therefore did not recommend nivolumab plus ipilimumab for use in the Cancer Drugs Fund.

Equality issues

There are no equality issues related to protected characteristics

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

- The condition is a preventable occupational-related disease, with higher incidence in areas of heavy industry. People with the condition may have lower socioeconomic status compared with people with other cancer types.
- People with the condition are often older and diagnosed at a late stage, when they can be too frail to travel for treatment, and 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 high prevalence 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. If recommended, the technology would be

available for all regardless of people's age, geographical location and socioeconomic status. Therefore the committee concluded that these are not equality issues.

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

3.29 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

It is uncertain whether nivolumab plus ipilimumab meets NICE's criteria for an innovative treatment

3.30 The company considered 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 the treatment of malignant pleural mesothelioma because it is the biggest advance in over a decade of research. The committee agreed that it reflected a step-change in treatment, but was aware that a technology is considered innovative only if it is associated with benefits not captured in the modelling. A clinical expert noted that the cost-effectiveness estimates may not capture the benefit of nivolumab plus ipilimumab in reducing the anger of people about having an occupational disease; however, the committee was not presented with this evidence. The committee concluded that the technology likely reflects a step-change in treatment, but did not identify benefits not captured by the company's economic modelling.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the

guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
August 2021

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.

Heather Stegenga
Technical lead

Yelan Guo
Technical adviser

Joanne Ekeledo

Project manager

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