NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

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

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

Issue date: July 2024

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 20 August 2024
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Durvalumab is not recommended, within its marketing authorisation, as neoadjuvant treatment with platinum-based chemotherapy, then alone as adjuvant treatment, for treating non-small-cell lung cancer (NSCLC) in adults whose cancer:

- is resectable (tumours 4 cm or over, or node positive) and
- has no epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

1.2 This recommendation is not intended to affect treatment with durvalumab 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 healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Usual treatment for resectable NSCLC in adults is nivolumab with chemotherapy then surgery. A resectable tumour is one that can be removed surgically.

Clinical trial evidence shows that, compared with placebo, durvalumab decreases the likelihood of:

- an event that would stop people having surgery (for example, the cancer getting worse), and
- their cancer coming back after surgery.

Durvalumab has not been directly compared in a clinical trial with usual treatment. The method used to compare durvalumab indirectly may not give a reliable estimate of how well it works compared with usual care.

The uncertainty in the clinical evidence means that the economic model is too uncertain to give reliable cost-effectiveness estimates. So durvalumab is not recommended.

2 Information about durvalumab

Marketing authorisation indication

2.1 Durvalumab (Imfinzi, AstraZeneca) with platinum-based chemotherapy as neoadjuvant treatment, and then as monotherapy after surgery, is indicated for 'the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.'

Dosage in the marketing authorisation

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

Price

2.3 The list price is £2,466 per 500-mg vial (excluding VAT; BNF online, accessed July 2024). The cost of a course of perioperative treatment of durvalumab is approximately £69,779.

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

3 Committee discussion

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

The condition

Treatment options and effects on quality of life

3.1 Standard care for resectable non-small-cell lung cancer (NSCLC) is surgical resection with neoadjuvant nivolumab with chemotherapy (referred to from here as neoadjuvant nivolumab). Other treatment options include neoadjuvant chemoradiotherapy and adjuvant chemotherapy which may be followed by maintenance treatment with atezolizumab through the Cancer Drugs Fund (CDF). Resectable NSCLC is usually considered to be early to locally advanced cancer, not including stage 3C. Surgery can cure the cancer, but recurrence is common and can either be locoregional (within the lungs and nearby lymph nodes) or distant metastatic (other part of the body). The patient organisation submission reported that if NSCLC recurs after surgery, it usually means that further curative treatment is unlikely. The patient expert explained that if NSCLC progresses to the metastatic stage, it results in a range of severe and distressing symptoms that affect all aspects of life. These include persistent chest infections, severe pain, mobility issues, and severe mental health issues for the patient and their carers and family. The patient organisation submission highlighted that in practice there is no way to tell if someone is cured other than waiting to see if the cancer does not come back, and this means there is continual anxiety for patients and carers that it will. The patient submission highlighted that patients want the best outcomes from chemoimmunotherapy treatment and that there was an unmet need to provide the best chance of cure for those with NSCLC. The committee considered that reducing the likelihood of recurrence was very important to patients, their carers and healthcare professionals. It concluded that new treatments that could achieve this would be welcomed.

Comparators

3.2 In its submission the company compared neoadjuvant durvalumab and chemotherapy followed by surgery and then adjuvant durvalumab monotherapy (referred to as perioperative durvalumab from here) to surgery alone, neoadjuvant nivolumab, and adjuvant chemotherapy. The final scope for this evaluation also included active monitoring and neoadjuvant chemoradiation therapy (nCRT). The EAG clinical expert considered that nCRT was not a relevant comparator because it would be used in a slightly different population who would not all be eligible for surgery. The clinical expert confirmed that nCRT is rarely offered because it is not very effective and has never been a popular or well implemented treatment choice. The CDF clinical lead thought that the only relevant comparator for this evaluation was neoadjuvant nivolumab, because people would only have active monitoring if they were not well enough to have neoadjuvant nivolumab, and these people would also not be well enough for perioperative durvalumab. They also explained that adjuvant treatments were not true comparators because the decision to have a neoadjuvant treatment or perioperative treatment regimen was made before surgery, which was a different decision to those taken after surgery. The committee concluded that neoadjuvant nivolumab was the most relevant comparator for this appraisal.

Clinical effectiveness

AEGEAN clinical trial evidence

3.3 The clinical evidence for perioperative durvalumab came from the AEGEAN randomised controlled trial. AEGEAN compared perioperative durvalumab with perioperative placebo (neoadjuvant chemotherapy and placebo followed by adjuvant placebo) in resectable NSCLC (stage 2A to 3B N2). The interim analysis used for the company submission was from

a November 2022 data cut and had a median follow-up of 11.7 months. The primary outcomes of the trial were:

- event-free survival (EFS), defined as the time from randomisation to a progression event that precluded surgery, progression after surgery, or death
- pathological complete response (pCR), defined as the absence of viable tumour cells in samples taken during surgery.

Overall survival was a key secondary outcome. Perioperative durvalumab was associated with a statistically significant improvement in EFS compared with perioperative placebo, with a hazard ratio of 0.68 (95% confidence interval [CI] 0.53 to 0.88). Perioperative durvalumab was also associated with a 13% improvement in pCR compared with placebo (95% CI 8.7 to 17.6%). No formal statistical analyses were done for the outcome of overall survival, in line with the trial's statistical analysis plan, but the company reported that median overall survival had not been reached for either arm of the trial. A descriptive summary of overall survival, which the company considers confidential so cannot be reported here, was provided to the committee. The committee considered that it had not seen formal evidence to support that perioperative durvalumab had a survival benefit compared with perioperative placebo, although it was aware that the overall survival data was immature. The committee noted that additional evidence from AEGEAN, if it were to become available, might reduce some of the uncertainty in the clinical evidence. It concluded that perioperative durvalumab was more effective than perioperative placebo at reducing the risk of recurrence of NSCLC after resection.

Generalisability

3.4 The EAG noted that biological sex, smoking status, programmed cell death ligand 1 (PD-L1) expression and lymph node station may be important treatment-effect modifiers for EFS and pCR. It thought these should be balanced with the NHS clinical practice population. The company submitted evidence from a clinical advisory board which stated that the AEGEAN trial population was generalisable to UK clinical practice. The advisory board noted that although there were differences in proportions for sex, squamous disease and lymph node station, it did not consider these to be a generalisability concern. The clinical expert stated that it was common for clinical trials to not reflect a clinical practice population exactly because trials tend to recruit younger, fitter people. They noted that sex was not considered an effect modifier for immunotherapies in practice, but added that there was uncertainty around this. They thought that disease stage would probably be a stronger effect modifier.

The CheckMate-816 trial compared neoadjuvant nivolumab with chemotherapy to neoadjuvant chemotherapy alone, and was used in the indirect comparisons (see section 3.6). The committee considered that CheckMate-816 had a different population to AEGEAN and that the differences in these populations would need to be accounted for. It noted that the company had adjusted the AEGEAN trial to compare perioperative durvalumab to neoadjuvant nivolumab and considered that the generalisability of the CheckMate-816 trial to both the AEGEAN trial and NHS clinical practice should also be considered. It noted that there were differences between the 2 trials in terms of numbers of people with different levels of PD-L1 expression. It also noted that there was variation in proportions of different disease stages at diagnosis between the 2 clinical trials and the proportions in the National Lung Cancer Audit (NLCA) 2024 report, which it considered to be a proxy for NHS clinical

practice. In particular, the CheckMate-816 trial had lower proportions of people with stage 3B disease. The clinical expert stated that CheckMate-816 was one of the earlier trials of neoadjuvant chemoimmunotherapy and would likely have had a more conservative approach to recruiting participants, including higher proportions of earlier stage disease. The committee questioned whether the median age in the AEGEAN trial (65 years) and the intervention arm of the CheckMate-816 trial (64 years) reflected the population that would be offered durvalumab in NHS clinical practice, as the median age in the NLCA 2024 report was 74. The clinical expert responded that the NLCA report covered all people with lung cancer in England, not just those eligible for surgery, so people in the report might be older on average than those who would have perioperative durvalumab in practice. They considered the age of people who would have perioperative durvalumab would be somewhere between that of the clinical trial and the NLCA report. The committee considered that the AEGEAN and CheckMate-816 trials broadly reflected the NHS clinical practice population. But it concluded that there were some key differences between both trials and NHS clinical practice (such as disease stage and age) that would need to be accounted for in the indirect treatment comparison (see section 3.6) and the modelling (see section 3.7).

Reporting of outcomes

3.5 The EAG noted that, of the outcomes included in the NICE final scope, only EFS, pCR and overall survival had been reported (with no formal reporting of overall survival). Other outcomes listed in the scope, including disease-free survival (DFS), adverse events, and health-related quality of life had not been reported. The EAG also noted that perioperative durvalumab had been compared to neoadjuvant nivolumab only for the outcome of EFS in the indirect treatment comparison (see section 3.6). The company clarification response stated that EFS was the most

appropriate outcome for a perioperative treatment that included a neoadjuvant component, as it included events that might prevent surgery (such as progression or adverse events), whereas DFS was only relevant to a particular subset of people who had surgery with complete resection. The committee noted this and felt that EFS was a more appropriate outcome for this appraisal than DFS. It concluded that, although it would have been preferable to see other outcomes from the scope reported and compared in the indirect treatment comparisons, including only EFS in these comparisons was sufficient for decision making.

Indirect treatment comparisons

3.6 There was no direct comparison of perioperative durvalumab with neoadjuvant nivolumab. The company did a matching-adjusted indirect comparison (MAIC) to compare perioperative durvalumab with neoadjuvant nivolumab. In the company base case, the AEGEAN trial population was adjusted to better match the CheckMate-816 trial population for all possible effect modifiers. The MAIC was used to generate a hazard ratio for the '0 to 3 month' period and the '3 month plus' period. Both MAICs, when compared with unadjusted comparisons, resulted in improved hazard ratios for perioperative durvalumab versus neoadjuvant nivolumab and versus the neoadjuvant chemotherapy arm of AEGEAN. The '3 month plus' hazard ratio was used to inform EFS in the model (see section 3.8). The committee recalled that there were differences between the AEGEAN population and the NHS clinical trial population in some important effect modifiers and considered that it was plausible that matching the AEGEAN population to the CheckMate-816 population would exaggerate some of these imbalances. Given that the EFS hazard ratios had a substantial effect on the cost-effectiveness model and its results, the committee was concerned that it had only seen 1 method of indirect comparison between perioperative durvalumab and neoadjuvant nivolumab, which had been adjusted to a target population

that may not reflect NHS clinical practice (see section 3.4). It considered that other methods, such as multilevel network meta-regression (ML-NMR) could have been used and could have generated estimates of the relative effectiveness of perioperative durvalumab compared with neoadjuvant nivolumab in more relevant populations (rather than one more similar to CheckMate-816). The committee considered that the current indirect treatment comparisons alone were not sufficient to inform decision making. It concluded that it would like to see supplementary approaches using ML-NMR explored to compare perioperative durvalumab with neoadjuvant nivolumab, adjusted to different target populations (including a population that would reflect NHS clinical practice and the AEGEAN population). This would highlight the impacts on the hazard ratios for EFS and the economic model output (see section 3.8).

Economic model

Company's model overview

3.7 The company constructed a state-transition model with 5 states to model the cost effectiveness of perioperative durvalumab compared with the comparators. The 5 health states were event free (EF), locoregional recurrence (LRR), distant metastases 1 (DM1), distant metastases 2 (DM2) and death. People in the model started in the EF health state and could either move to LRR or DM1. From LRR people could move to DM1 and from DM1 they could move to DM2. People could transition to the death health state from any of the other health states. The model included a cure assumption, which meant that a proportion of people in the EF health state at a given time point would be considered cured (see section 3.15). The DM1 and DM2 health states were modelled using a partitioned survival model nested inside the state-transition model (see section 3.12). People in the model accrued quality-adjusted life years (QALYs), treatment costs and healthcare resource use costs depending on which treatments they had and which health states they spent time in. The

intervention arm of the model (perioperative durvalumab or neoadjuvant nivolumab) did not affect the efficacy of subsequent treatments or the costs or utilities generated in subsequent health states. It only informed transitions into subsequent health states and affected what types of treatment people could have in them due to immunotherapy retreatment considerations (see section 3.14). The committee considered that the model structure was appropriate for decision making. But it noted that starting age could have a substantial effect on total QALYs, and concluded that the starting age of the model should be set to 70 years in line with the likely NHS clinical practice population (see section 3.4)

Modelling event-free survival

3.8 The company used a pooled EFS curve from both arms of the AEGEAN trial, censored for non-death events, to inform transitions from the EF state to the death state. This assumed that transitions from EF to death were not dependent on which treatment people had in the model. For other transitions out of the EF state, the company used the EFS curves from the clinical trials (see section 3.3). It used a piecewise approach for this, using different approaches for the first 3 months and from 3 months onwards. The company censored the EFS Kaplan–Meier curve for perioperative placebo from AEGEAN for all death events (so that it only represented progression to LRR or DM1), and used this directly to inform transition probabilities for all interventions for the first 3 months. From 3 months, the company extrapolated the neoadjuvant chemotherapy EFS curve to the time horizon of the model with a log-normal distribution. It applied the hazard ratios from the MAIC (see section 3.6) and CheckMate-816 to the extrapolated neoadjuvant chemotherapy EFS curve to generate curves for perioperative durvalumab and neoadjuvant nivolumab respectively. The company used these curves to calculate the per-cycle transition probabilities out of the EF state, and assumed that these transitions would be split by a fixed percentage between LRR and

DM1, based on clinical opinion. It also provided a scenario in which the split was based on the AEGEAN trial proportions. The company considers the modelled and trial-observed proportions to be confidential so they cannot be reported here.

The EAG noted that the proportions of EFS events split between LRR and DM1 in the base case were opposite to what was seen in the AEGEAN trial (with more recurrence to metastatic disease). It also noted that the proportions were both time constant and treatment independent, which was inconsistent with the clinical advice they had received. The EAG requested scenarios to explore the effect of modelling both time- and treatment-dependent probabilities of moving to LRR and DM1. The company acknowledged the potential of transitions from EF to LRR and DM1 to be affected by treatment and time but did not provide these scenarios, stating that there was insufficient evidence to inform them. The clinical expert explained that the assumed split was based on longstanding historical experience with resectable NSCLC, but also considered that treatment with immunotherapies would probably result in fewer people having distant metastatic recurrence and more having locoregional recurrence. The committee considered that the clinical expert figures were based on historical experience without immunotherapies, and if immunotherapies were likely to reduce the proportion of recurrence to metastatic disease, it would be appropriate to reflect this in the modelling. The committee noted that changing the proportions did not have a large effect on the cost-effectiveness estimates but concluded that it preferred to model transitions out of EF based on the proportions seen in the AEGEAN trial.

Longer-term treatment effects

3.9 The company used a piecewise approach (see section 3.8) because of the delayed separation of the EFS curves in the AEGEAN trial (until

3 months) and because there was evidence of proportional hazards in the trial during the 3-month-plus period (but proportional hazards were not supported in the overall trial period). The EAG noted that the piecewise approach applied constant hazard ratios for perioperative durvalumab and neoadjuvant nivolumab to the neoadjuvant chemotherapy reference curve from 3 months to the time horizon of the model. This assumed proportional hazards between perioperative durvalumab and neoadjuvant nivolumab for the lifetime of the model, even though evidence was not submitted to support this. The EAG requested at clarification that the company explore a parametric network meta-analysis, providing time-varying hazard ratios for both comparators, as a scenario analysis. The company responded that this approach required survival distributions fitted to the overall trial period of AEGEAN, which resulted in poorly fitting curves. The EAG acknowledged this but considered that applying a fixed hazard ratio might be as much of a problem as poorly fitting curves, and thought both should be explored. The committee considered that because most people in the EF state at 5 years remained there indefinitely (see section 3.15), the model was very sensitive to the EFS hazard ratios up to 5 years. It considered that modelling constant hazard ratios for perioperative durvalumab and neoadjuvant nivolumab versus neoadjuvant chemotherapy assumed a proportional relationship between perioperative durvalumab and neoadjuvant nivolumab beyond the observed data. This brought uncertainty to the model and could bias it, although the direction of the potential bias was unclear. It concluded that it wanted to see the proportional hazards assumption relaxed, and time varying-hazard ratios fully explored. This would allow the uncertainty in the treatment effect estimates, derived from potential changes to the underlying hazards, to be better explored.

Treatment effect waning

3.10 The EAG also thought that the proportional hazards approach might implicitly exclude the possibility of treatment effect waning, whereby the treatment effects of perioperative durvalumab and neoadjuvant nivolumab might fall once people stop taking the drugs. The EAG requested scenario analyses at clarification to explore additional modelling of treatment effect waning at different time points. The company did not do this, because it considered that there was no evidence of treatment effect waning in its data, which had a maximum follow up of 3 years. The CDF clinical lead explained that in many trials of immunotherapies for metastatic NSCLC (which are now quite mature) there was no substantial evidence of treatment effect waning, and agreed with the company that if waning of treatment effect were to occur it would likely be visible in the company's data. The clinical expert also thought that there was not likely to be a waning of treatment effect beyond the observed data. The committee acknowledged the evidence, but noted that there was no longer-term evidence supporting the presence or absence of treatment effect waning in the NSCLC perioperative setting. The committee considered that treatment effect waning was only likely to have a substantial effect on the cost effectiveness results of the model if it occurred before the cure point (see section 3.15). It concluded that additional modelling of treatment effect waning would be less important in scenarios that applied a cure-assumption and that explored time-varying hazard ratios in the NMA (see section 3.9). But it also noted that in the scenarios that did not apply a cure assumption (see section 3.15), additional treatment effect waning should be explored.

Modelling locoregional recurrence

3.11 People in the LRR health state in the model could either have concurrent chemoradiotherapy (cCRT) followed by durvalumab maintenance treatment, cCRT alone, radiotherapy, or best supportive care. The model

assumed that people having best supportive care could only transition to the death state. The company used extrapolations of the progression-free survival and time-to-progression curves from the PACIFIC trial (a randomised controlled trial that compared cCRT alone with cCRT followed by durvalumab maintenance treatment) to inform transitions out of the LRR health state. The company used a hazard ratio from the external literature to generate transitions for radiotherapy alone. The transition probabilities were weighted by market share depending on whether or not someone was eligible for treatment with an immunotherapy (see section 3.14). The transition probabilities from LRR to death were further weighted between the PACIFIC trial-derived probabilities and those derived from the overall survival curve from a study by Wong et al. This was to represent people who had best supportive care in the LRR health state and who were assumed to only transition to the death health state. The EAG questioned whether it was reasonable to assume that people in the LRR state could only transition to the death state. The clinical expert explained that people who have best supportive care for NSCLC at the LRR disease stage are generally very unwell and will have very poor outcomes; their disease would progress to distant metastases but it was likely that they would die soon afterwards. The committee considered that the assumption to only model transitions from LRR to death was a simplification but that it broadly reflected the disease course and was suitable for decision making. The committee concluded that the modelling of transitions from the LRR health state was appropriate.

Modelling distant metastases

3.12 The company used a nested partitioned survival model to model the health effects and costs accrued for each treatment arm in the DM1 and DM2 health states. It reproduced the progression-free survival and overall survival extrapolations for immunotherapies and chemotherapies from the models from the NICE technology appraisals of pembrolizumab with

pemetrexed and platinum chemotherapy (TA683), pembrolizumab with carboplatin and paclitaxel (TA770) and pembrolizumab monotherapy (TA531). Atezolizumab regimens were assumed to have equivalent efficacy to their counterpart pembrolizumab regimens, and best supportive care was modelled from the Wong et al. study for overall survival only. Progression-free survival was used to inform the split of people in the model between the DM1 and DM2 health states (and associated costs and QALYs). Overall survival was used to inform the transition probabilities to the death health state. The transition probabilities were weighted by market share, which depended on whether or not people were eligible for immunotherapy retreatment (see section 3.14). The committee concluded that the modelling of the distant metastases states was appropriate for decision making.

Transitions out of LRR and DM1

3.13 The EAG noted that the transitions out of the LRR and DM1 health states (see sections 3.11 and 3.12) were applied as a function of model time and not of time spent in the health states. This would mean that a person in the model who entered the LRR health state in cycle 40, would have the relevant transition probabilities (derived from the PACIFIC trial) for cycle 40, even though it was their first cycle in that health state. The EAG noted that it would be possible to use tunnel states to model transitions as a function of health-state occupancy rather than model cycle. The company responded that a very large number of tunnel states would be needed. It stated that the approach it had taken was for computational simplicity and that it was a common simplification seen in health economic modelling. The committee considered that having time-independent transition probabilities from these health states added uncertainty to the modelling, but that the direction and extent of any bias was unclear. It noted this that this simplification was often used in complex state-transition models and concluded that modelling time-independent

transition probabilities from the LRR and DM1 health states, while not the ideal approach, was acceptable for decision making.

Immunotherapy retreatment

3.14 The company model permitted people who had an immunotherapy before or after surgery to have retreatment with an immunotherapy in the LRR (see section 3.11) or DM1 (see section 3.12) health states. This was allowed if their NSCLC had progressed 6 months or more after finishing perioperative durvalumab or neoadjuvant nivolumab. Not all eligible people would have retreatment with immunotherapy because some people may be too unwell. The model assumed that 70% (based on the NICE technology appraisal guidance durvalumab for maintenance treatment of unresectable NSCLC after platinum-based chemoradiation, TA798) and 80% (based on TA683 and TA770) of eligible people would have immunotherapies at the LRR and DM1 states respectively, and that these people would not experience any reduced efficacy of immunotherapy due to retreatment. The clinical expert stated that in practice people had regular scans and progression was picked up relatively quickly so they would expect upwards of 60% of eligible people to have retreatment with an immunotherapy at a later disease stage. But they thought that 70% to 80% might be slightly too high an estimate. They also explained that, as eligible people's cancer had progressed 6 months or more after finishing immunotherapy treatment, their NSCLC would still be considered to be 'immunotherapy sensitive' and that they would not expect treatment effectiveness to fall, although they noted there was uncertainty around this. The CDF clinical lead explained that because neoadjuvant nivolumab was only recently recommended, numbers accessing retreatment were still very low and it was difficult to provide accurate figures or evidence on retreatment efficacy. The committee considered that it was appropriate to model a 6-month progression restriction before retreatment was allowed but that in the absence of

evidence from practice, the modelled proportions of eligible people accessing treatment may be too high. It preferred to model 60% as having retreatment with immunotherapy at subsequent stages. The committee concluded that there was limited evidence on the efficacy of immunotherapy retreatment and that this issue was associated with unresolved uncertainty in the modelling.

Modelling of cure

3.15 The company base case included a structural assumption of cure, under which 95% of people who were in the EF state at 5 years were considered cured, no longer had any risk of disease progression and were modelled as having general population mortality. The company reported that the cure point and portion was informed by a clinical expert advisory board and was broadly aligned with previous appraisals of resectable and resected NSCLC such as the NICE technology appraisal guidance on nivolumab with chemotherapy for neoadjuvant treatment of resectable NSCLC (TA876), atezolizumab for adjuvant treatment of resected NSCLC (TA823) and osimertinib for adjuvant treatment of EGFR mutation-positive NSCLC after complete tumour resection (TA761).The EAG noted this but recalled the position of the EAG on TA876, which was that there was no convincing evidence to support how the cure assumption was modelled. It noted that the company did not provide scenarios exploring different cure points and proportions. The EAG submitted base cases both with and without cure. The clinical expert confirmed that in practice, people were followed for up to 5 years after surgery and that they considered the cure point and proportion to be realistic in this sense. The committee noted that there was little evidence to inform the time point and cure proportions. It also considered that further data cuts or updated indirect treatment comparisons could provide additional evidence on modelling of a cure assumption. The committee considered that it was likely to be appropriate to model a cure assumption in some form, although this was uncertain. It

considered that ideally this would be informed directly by clinical data. It concluded that, in the absence of clinical data, the company should provide scenarios exploring different time points and proportions assumed to be cured as well as scenarios without a cure assumption.

Utility values

Source of utility values

3.16 The AEGEAN trial had limited follow-up data on utilities in health states after EF. So, the company used the EF utility value from the AEGEAN trial to inform the EF health state and a utility value from the PACIFIC trial for the LRR health state (these are considered confidential and cannot be reported here). The progression free (0.759) and progressed disease (0.662) utility values from the KEYNOTE-189 trial informed the DM1 and DM2 health states respectively. The company noted that the EF utility value from AEGEAN was slightly higher than the age-matched utility value for the general population (0.829). The company kept the AEGEAN EF utility value in its base case but provided a scenario using the general population value. The EAG noted that the decrement in utility from EF to DM1 was smaller than it would expect and was similar to what would be expected from the EF to LRR health states. So, the EAG produced a scenario using the age-matched utility from the general population for EF, then a fixed decrement of 0.2 to generate a utility value for LRR, before generating utility values for DM1 and DM2 by maintaining the absolute decrements from the company base case and applying them to the EAG's modified LRR value. This gave lower utility values in each health state than in the company base case. The patient expert stated that in their personal experience, utility values for metastatic disease were likely to be lower than the values in the company base case. The committee considered that it was not reasonable to model a utility value for the EF state that was higher than that of the general population and that the decrement in utility from EF (which can be asymptomatic) to DM1 and

DM2, which can have severe symptoms (see section 3.1), was likely to be too small. The committee concluded that it would prefer to use the EAG's decrement scenario for decision making.

Cost-effectiveness estimates

Committee's preferred assumptions

3.17 The committee recalled its preferences for the cost-effectiveness modelling of perioperative durvalumab including:

- neoadjuvant nivolumab being the most relevant comparator (section 3.2)
- setting the model starting age to 70 years (see section 3.7)
- assuming that transitions from the EF to the LRR and DM health states are split in line with the AEGEAN trial (see section 3.8)
- assuming that people in the model who have best supportive care in the LRR health state do not transition to DM1 (see section 3.11)
- using the company's nested partitioned survival model to estimate costs and QALYs for the DM health states (see section 3.12)
- modelling health state occupancy time-independent transitions out of the LRR and DM health states as a simplifying approach (see section 3.13)
- assuming that 60% of people eligible for immunotherapy treatment in the LRR and DM1 health states will have it (see section 3.14)
- using the EAG's decrement scenario to model utility (see section 3.16).

The committee noted that there was a substantial difference between the deterministic and probabilistic ICERs in the company and EAG base cases. It also recalled the substantial uncertainty around the company's cost-effectiveness model, including:

- the indirect treatment comparison methodology and the EFS hazard ratio (see section 3.6)
- the appropriateness of a proportional hazards assumption and the maintenance of treatment effect beyond the observed data (see section 3.9)
- whether it is appropriate to include a cure assumption, and the time point and cure proportion modelled (see section 3.15).

It considered that until these uncertainties were addressed through further analyses it was unable to establish a plausible incremental cost-effectiveness ratio (ICER) for perioperative durvalumab as a treatment for resectable NSCLC. The committee also noted that further data from the AEGEAN trial, if available, might help to resolve some of the uncertainty in the modelling.

Other factors

Equality

3.18 The committee did not identify any equality issues.

Uncaptured benefits

3.19 The committee considered if perioperative durvalumab was innovative. It did not identify additional benefits not captured in the economic modelling. So, the committee concluded that all additional benefits of perioperative durvalumab had already been taken into account.

Conclusion

Recommendation

3.20 The committee took into account its preferred assumptions, the key uncertainties in the modelling and additional analyses that it needed to see to explore these uncertainties. With the current analyses, it could not

conclude that perioperative durvalumab represented a cost-effective use of NHS resources, and stated that further analyses were needed to inform decision making. So, perioperative durvalumab was not recommended for treating resectable NSCLC.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

James Fotheringham

Vice Chair, technology appraisal committee A

NICE project team

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

Samuel Slayen

Technical lead

Christian Griffiths

Technical adviser

Leena Issa

Project manager

ISBN: [to be added at publication]