

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

Technology appraisal guidance

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1 Recommendation

1.1 Durvalumab is recommended, within its marketing authorisation, as neoadjuvant treatment with platinum-based chemotherapy, then continued 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.

Durvalumab is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

Usual treatment for resectable NSCLC 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 with platinum-based chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) decreases the likelihood of:

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

Durvalumab has not been directly compared in a clinical trial with usual treatment. An indirect comparison suggests that neoadjuvant and then adjuvant durvalumab may reduce the likelihood of the cancer getting worse or coming back after surgery compared with neoadjuvant nivolumab, but this is uncertain.

The cost-effectiveness estimates for neoadjuvant and then adjuvant durvalumab compared with neoadjuvant nivolumab and chemotherapy are within the range NICE

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer (TA1030)

considers an acceptable use of NHS resources. So, perioperative durvalumab with chemotherapy is 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 \geq 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. 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 plus 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 (in another 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 NHS England 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 AEGEAN, a phase 3, double-blind, 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 company initially submitted an interim analysis from a November 2022 data cut with a median follow up of 11.7 months. During consultation on the draft guidance the company provided an updated interim analysis, from May 2024 with 25.9 months median follow up. 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 (OS) was a key secondary outcome.

At the second interim analysis perioperative durvalumab was associated with a statistically significant improvement in EFS compared with perioperative placebo, with a hazard ratio of 0.69 (95% confidence interval [CI] 0.55 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 OS, in line with the trial's statistical analysis plan, but the company provided a descriptive summary of OS at both interim analyses. At the first meeting the committee considered that it had not seen formal evidence to support that perioperative durvalumab had an OS benefit compared with perioperative placebo, but it acknowledged that the OS data was immature. At the second interim analysis, perioperative durvalumab was associated with numerically greater OS compared with perioperative placebo, although this did not reach statistical significance. The hazard ratio was 0.89 (95% CI 0.70 to 1.14). The committee noted the updated evidence from AEGEAN but considered that it was still immature. So, the committee still considered that it had seen no convincing evidence to suggest that perioperative durvalumab had an OS advantage compared with perioperative placebo. 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 reflect the NHS clinical practice population. The company submitted evidence from a clinical advisory board that stated that the AEGEAN trial population was generalisable to UK clinical practice. The advisory board noted that although there were differences

between the AEGEAN trial and UK clinical practice in proportions of 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.

CheckMate-816 was a phase 3 randomised controlled trial that compared neoadjuvant nivolumab with chemotherapy to neoadjuvant chemotherapy alone. CheckMate-816 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 with 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 were reweighted to better match the resectable NSCLC population). The committee considered the NLCA report 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 people, including higher proportions of earlier-stage disease. At the first meeting 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 report was 74 years. 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 [sections 3.6 and 3.7](#)) and the modelling (see [section 3.11](#)).

Reporting outcomes

- 3.5 The EAG noted that the company did not report disease-free survival (DFS) with its original submission for the first meeting but did provide it as part of the second interim analysis (see [section 3.3](#)). The EAG also noted that perioperative durvalumab had been compared with neoadjuvant nivolumab only for the outcome of EFS in the indirect treatment comparisons (see [section 3.6](#) and [section 3.9](#)). The company clarification response stated that EFS was the most appropriate outcome for a perioperative treatment that included a neoadjuvant component. It said that this was because EFS 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 evaluation than DFS. It concluded that, although it would have been preferable to see other outcomes from the scope compared in the indirect treatment comparisons, including only EFS in these comparisons was sufficient for decision making.

Indirect treatment comparisons

Matching-adjusted indirect comparison

- 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 (further below 1) for perioperative durvalumab compared with neoadjuvant nivolumab and compared with the neoadjuvant chemotherapy arm of AEGEAN. The MAIC was updated before the second meeting using the EFS results from the second interim analysis. Only the '3 month plus' hazard ratio was used to inform EFS in the model (see [section 3.12](#)). At the first meeting the committee noted 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 differences. 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). 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 3.12](#)).

Multilevel network meta-regression

- 3.7 During consultation on the draft guidance, the company did a feasibility assessment for an ML-NMR to compare perioperative durvalumab with all of the comparators in the NICE scope. The company reported that some of the included trials had limited reporting of baseline characteristics (some of which were possible effect modifiers, that is, characteristics that could affect how well the treatment works). It also said that there were differences in the staging systems used in some trials. The company highlighted that only the baseline characteristics that were available across all studies (sex, region, planned

platinum chemotherapy and histology) could be included in the ML-NMR. It considered that excluding several potentially important effect modifiers would be a substantial limitation of this approach. The company also suggested that an ML-NMR would need individual patient data from included trials or extensive aggregate data from a larger number of trials (which was not available in this case), or would have to rely on the assumption of shared-effect modification. This would assume that any effect modifiers would work in roughly the same way for the different interventions in the network. The company stated that an ML-NMR was unsuitable, because:

- the different interventions in the network were from different classes (surgery, chemotherapy, and immunotherapy with chemotherapy)
- even perioperative durvalumab and neoadjuvant nivolumab, being in the same class, had differences in the type of regimen (for example, number of administrations), and subgroup analyses suggested the possibility of variation in modification of effects
- the assumption of shared-effect modification is a strong one, and it was not possible to test it with adequate power.

The EAG suggested that shared-effect modification was likely to be a strong assumption and would limit any ML-NMR analyses. But it highlighted that the alternative was to use 2 different analyses for the different comparators. The company stated that, as neoadjuvant nivolumab was the most relevant comparator (see section 3.2), either the MAIC or multivariate network meta-analysis (NMA; see [section 3.6](#) and [section 3.9](#)), each of which compared perioperative durvalumab with neoadjuvant nivolumab, would be the most relevant analysis. It considered that an all-encompassing ML-NMR was not feasible or necessary. The committee acknowledged that any ML-NMR would have to rely on the shared-effect modifier assumption and that there was no clear evidence to support this for the network of comparators. It concluded that it was satisfied with the company's justification for not doing an ML-NMR.

Piecewise approach to modelling relative efficacy

3.8 The company used a piecewise approach to modelling EFS (see [section 3.12](#)). This was because there was:

- delayed separation of the EFS curves in the AEGEAN trial (until 3 months), and
- 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 both 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 NMA, providing time-varying hazard ratios for both comparators, as a scenario analysis. The company responded that this approach needed survival distributions to be 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 event-free state at 5 years remained there indefinitely (see [section 3.18](#)), 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 compared with neoadjuvant chemotherapy assumed a proportional relationship between perioperative durvalumab and neoadjuvant nivolumab beyond the observed data. The committee considered that this brought uncertainty to the model and could bias it, although the direction of the potential bias was unclear. At the first meeting the committee 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.

Time-varying multivariate approach to modelling relative efficacy

3.9 The company did a multivariate NMA to compare EFS for perioperative durvalumab with neoadjuvant nivolumab using time-varying hazard ratios. It only reported the fixed-effects model because the credible intervals for the random-effects model were too wide for it to be useful. The company considers the exact results of the multivariate NMA to be confidential, so they cannot be reported here, but it considered that time-constant hazard ratios was a conservative choice. The company suggested that the log-normal was the most appropriate distribution to fit to the data from AEGEAN and CheckMate-816. The EAG highlighted that the Gompertz distribution, while a better fit statistically and visually, resulted in an implausible hazard ratio over time and so it considered that the log-normal was a reasonable choice. The company provided the functionality in the model for the relative effectiveness of perioperative durvalumab compared with neoadjuvant nivolumab on EFS (see [section 3.5](#)) to be informed by either time-constant (see [section 3.8](#)) or time-varying hazard ratios. The committee thought that both approaches may give plausible estimates of the relative effectiveness of perioperative durvalumab compared with neoadjuvant nivolumab but that both were associated with uncertainty. It noted that both the company and the EAG had used the time-constant hazard ratios in their base cases and that both considered that doing so may be a conservative assumption. The committee considered that the time-varying hazard ratio might be the less plausible of the 2 and concluded that it would prefer to use the time-constant hazard ratio.

Economic model

Company's model overview

3.10 The company created 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 move to either 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 3.18](#)). The DM1 and DM2 health states were modelled using a partitioned-survival model nested inside the state-transition model (see [section 3.15](#)). 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 because of immunotherapy retreatment considerations (see [section 3.17](#)). The committee recalled its concerns about immature OS data (see [section 3.3](#)) and noted that OS from the model was informed indirectly from external sources. It considered that the model relied on a type of surrogate relationship between EFS and OS and that, while this was plausible, the magnitude of this relationship was highly uncertain. The committee had seen no evidence on correlation between the 2 endpoints to show that changes in EFS resulted in proportionate changes to OS. It considered that this brought uncertainty to the analysis and results but concluded that the model was broadly appropriate for decision making.

Model starting age

- 3.11 In the first meeting, the committee noted that starting age could have a substantial effect on total QALYs, and concluded that the starting age of the model should be in line with the likely NHS clinical practice population (see [section 3.4](#)). The company disagreed with the committee's conclusion at the first meeting that there were differences in average age that needed to be accounted for between the presumed NHS clinical practice population and the AEGEAN trial population. The company noted that their clinical expert opinion suggested that the median age in the AEGEAN trial (65 years) was generalisable to NHS clinical practice and it retained this starting age in its base case. At the second meeting, the CDF clinical lead stated that data from NHS practice showed that after [NICE's technology appraisal guidance on nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer](#) was published in March 2023,

876 people with resectable NSCLC had accessed neoadjuvant nivolumab with a mean age of 67.3 years. The committee considered that the data from the CDF clinical lead was from the relevant NHS practice population that might access perioperative durvalumab if it were recommended. So, it concluded that the starting age of the model should be set to 67.3 years.

Modelling event-free survival

3.12 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 option 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 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](#)) or the multivariate NMA (see [section 3.9](#)) 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 it 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 long-standing 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. It preferred to model transitions out of EF based on the proportions seen in the AEGEAN trial. The company updated its base case for the second committee meeting to use the proportions from the AEGEAN trial. The committee concluded that this was appropriate for decision making.

Treatment-effect waning

3.13 The EAG suggested 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 at the first meeting 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 3.18](#)). It concluded at the first meeting that it would be less important to do additional modelling of treatment-effect waning in scenarios in which a cure assumption was applied and an NMA was done to generate time-varying hazard ratios (see [section 3.9](#)).

But it noted that in the scenarios that did not apply a cure assumption (see [section 3.18](#)), additional treatment-effect waning should be explored. During consultation on the draft guidance the company did not model treatment-effect waning. It justified this by stating that the second interim analysis of the AEGEAN trial had a maximum follow up of 5 years, and treatment effect appeared to be relatively constant up to 5 years. The committee noted the low numbers of people at risk towards the end of the trial, which it considered brought uncertainty to this assumption. But it also recalled its conclusion from the first meeting that treatment-effect waning would be less important if a cure was modelled and time-varying hazard ratios were explored. The committee concluded that it was plausible that the treatment effect of perioperative durvalumab compared with neoadjuvant nivolumab might wane over time, but that this probably would not have a major effect on the cost-effectiveness results. It concluded that the company's base case, which did not apply treatment-effect waning, was acceptable for decision making.

Modelling locoregional recurrence

3.14 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 to inform transitions out of the LRR health state. PACIFIC was a phase 3, double-blind, randomised controlled trial that compared cCRT alone with cCRT followed by durvalumab maintenance treatment. 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 3.17](#)). The transition probabilities from LRR to death were further weighted between the PACIFIC trial-derived probabilities and those derived from the OS curve from a study by Wong et al. (2016). 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

- 3.15 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 OS extrapolations for immunotherapies and chemotherapies from the models from the [NICE technology appraisal guidance on 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 OS 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). OS 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 3.17](#)). The committee concluded that the modelling of the distant metastases states was appropriate for decision making.

Transitions out of LRR and DM1

3.16 The EAG noted that the transitions out of the LRR and DM1 health states (see [sections 3.14 and 3.15](#)) 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

3.17 The company model permitted people who had an immunotherapy before or after surgery to have retreatment with an immunotherapy in the LRR (see [section 3.14](#)) or DM1 (see [section 3.15](#)) 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 [NICE's technology appraisal guidance on durvalumab for maintenance treatment of unresectable NSCLC after platinum-based](#)

chemoradiation) 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 because of 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 that there was uncertainty around this. The CDF clinical lead explained that because neoadjuvant nivolumab was only recently recommended, numbers of people 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 cure

- 3.18 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 [NICE's 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 up 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 to inform the modelling of a cure assumption. The committee considered that it was likely to be appropriate to model a cure assumption in some form, but 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.

For the second meeting, the company provided scenario analyses exploring:

- a 5-year cure time point with a 12-month warm up (a gradual increase of cure proportion from 0% to 95% between years 5 and 6)
- a 6-year cure time point
- no cure applied.

The EAG provided additional scenarios that explored a 5-year cure time point with warm-up periods of 24 and 60 months. The committee maintained its position from the first meeting that cure should ideally be modelled directly from clinical data. The EAG explained that a clinical trial with a very long follow up would be needed to do this and the committee acknowledged this. In the absence of such evidence, the committee acknowledged that the 95% cure proportion at 5 years was in keeping with clinical opinion and previous evaluations in this disease area. It concluded that there was considerable uncertainty associated with this assumption but that it would use the company's modelling of cure for decision making.

Utility values

Source of utility values

3.19 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 (which compared pembrolizumab and chemotherapy with placebo) 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. It also considered 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

Acceptable ICER

3.20 [NICE's manual on health technology evaluations](#) notes that, above a most

plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. The committee noted the remaining uncertainty, specifically around:

- the relative effectiveness of perioperative durvalumab compared with neoadjuvant nivolumab in terms of EFS and how long any treatment effect would last (see [section 3.13](#))
- the modelling of the assumption of cure (see [section 3.18](#))
- the absence of a statistically significant improvement for perioperative durvalumab compared with placebo for OS, and the reliance of the modelling on an uncertain surrogate relationship between EFS and OS (see [section 3.3](#) and [section 3.10](#)).

So, the committee concluded that an acceptable ICER would be towards the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions

3.21 The committee recalled its preferences for the cost-effectiveness modelling of perioperative durvalumab from the first meeting, including:

- neoadjuvant nivolumab being the most relevant comparator (see [section 3.2](#))
- assuming that transitions from the EF to the LRR and DM health states were split in line with the AEGEAN trial (see [section 3.12](#))
- assuming that people in the model who have best supportive care in the LRR health state do not transition to DM1 (see [section 3.14](#))
- using the company's nested partitioned-survival model to estimate costs and QALYs for the DM health states (see [section 3.15](#))

- modelling health-state occupancy time-independent transitions out of the LRR and DM health states as a simplifying approach (see [section 3.16](#))
- assuming that 60% of people eligible for immunotherapy treatment in the LRR and DM1 health states will have it (see [section 3.17](#))
- using the EAG's decrement scenario to model utility (see [section 3.19](#)).

The committee also noted its preferences for the cost-effectiveness modelling from the second committee meeting, including:

- using the time-constant hazard ratios from the MAIC to model the relative effectiveness of perioperative durvalumab compared with neoadjuvant nivolumab (see [section 3.9](#))
- modelling cure using a 5-year cure time point and a 95% cure proportion (see [section 3.18](#))
- using a model starting age of 67.3 years to reflect the population of people in NHS clinical practice who have resectable NSCLC (see [section 3.11](#))
- not applying treatment-effect waning to the model (see [section 3.13](#)).

Other factors

Equality

3.22 The committee did not identify any equality issues.

Uncaptured benefits

3.23 The committee considered whether there were any uncaptured benefits of durvalumab. It did not identify additional benefits of durvalumab 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

- 3.24 The committee took into account its preferred assumptions and the key uncertainties in the modelling. It concluded that the most plausible ICER was within the range considered an acceptable use of NHS resources. So, perioperative durvalumab is recommended for routine commissioning.

4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has resectable non-small-cell lung cancer and the healthcare professional responsible for their care thinks that perioperative durvalumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer (TA1030)

Ian Watson

Associate director

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