Single Technology Appraisal

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Astrazeneca**
   a. Additional evidence

2. **External Assessment Group critique of company comments on the Draft Guidance**
   a. Factual accuracy check

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 20 August 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted] [redacted], AstraZeneca UK

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	**Summary** At the second interim analysis of the AEGEAN study (data cutoff 10 May 2024), the event-free survival hazard ratio of perioperative durvalumab compared with perioperative placebo remained consistent with the first interim analysis (0.69 [95% confidence interval 0.55 to 0.88]), and a sustained event-free survival benefit continued to be observed at key landmark survival timepoints (12, 24, and 36 months).Disease-free survival data were available at the second interim analysis and demonstrated a continued survival benefit of perioperative durvalumab in the adjuvant setting. The disease-free survival hazard ratio was 0.66 (95% confidence interval 0.47 to 0.92; p-value 0.013652). An additional descriptive overall survival analysis further supported the survival benefit of perioperative durvalumab, with an overall survival hazard ratio at the second interim analysis of 0.89 (95% confidence interval 0.70 to 1.14). The committee indicated in the draft guidance document that further exploration regarding the indirect treatment comparisons was required, therefore, to support the committee with decision making, the company explored the feasibility of conducting a multilevel network meta-regression and analyses to assess the uncertainty of the matching-adjusted indirect comparison results, using the data from the second interim analysis. On completion of the feasibility assessment of conducting a multilevel network meta-regression, it was determined inappropriate to conduct the analysis as heterogeneity of effect modifiers existed, the treatments in the network differed with respect to drug class and/or regimen, and the data available were sparse. Exploration of time-varying hazard ratios in the matching-adjusted indirect comparison were conducted to further understand the uncertainty of the constant hazard ratio approach for perioperative durvalumab compared with neoadjuvant nivolumab from 3-months onwards (second interim analysis hazard ratio = [redacted]; 95% confidence interval [redacted] to [redacted]). The time-varying hazard ratios decreased to a hazard ratio of [redacted] at approximately 6 months, where the hazard ratio for perioperative durvalumab versus neoadjuvant nivolumab stabilised from this point onwards. The matching-adjusted indirect comparison was concluded as the most robust and appropriate indirect treatment comparison to inform decision making, due to the ability to suitably adjust for expected treatment-effect modifiers. The CheckMate 816 trial population was considered generalisable to UK clinical practice in TA876 and thus was considered an appropriate population to match to.[1] The consistency of the treatment benefit of perioperative durvalumab versus neoadjuvant nivolumab observed across both constant and time-varying approaches further supported the matching-adjusted indirect comparison as the preferred approach. The time-varying matching-adjusted indirect comparison HRs also justified the use of the piecewise modelling approach applied in the company submission. Neoadjuvant nivolumab remains the principal comparator for this appraisal. When applying a constant matching-adjusted indirect comparison hazard ratio, the ICER for perioperative durvalumab versus neoadjuvant nivolumab is £5,374 per QALY gained; when applying time-varying matching-adjusted indirect comparison hazard ratios, perioperative durvalumab dominates neoadjuvant nivolumab (Table 1). The ICERs presented in Table 1 below are based on second interim analysis of AEGEAN and the following NICE preferred assumptions: • Proportion of patients entering the LRR and DM states aligned to the AEGEAN trial

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<table>
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60% immunotherapy in LRR and DM1
EAG utility scenario

<table>
<tr><th>Matching-adjusted indirect comparison scenario</th><th>ICER (perioperative durvalumab versus neoadjuvant nivolumab + PDC)</th></tr>
<tr><td>Base case (constant hazard ratios)</td><td>£5,374</td></tr>
<tr><td>Time-varying hazard ratios</td><td>Durvalumab dominates</td></tr>
</table>
<u>At a willingness-to-pay threshold of £20,000 per QALY gained, perioperative durvalumab remains highly cost-effective versus neoadjuvant nivolumab, regardless of MAIC methodology applied.</u>
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<tr><td>2</td><td>
Survival data from the recent second interim analysis of the AEGEAN study further confirms the survival benefit of perioperative durvalumab observed at the first interim analysis

To address the committee’s concern regarding uncertainty in the clinical evidence for a survival benefit for perioperative durvalumab, we have provided the results from the recent second interim analysis (data cutoff 10 May 2024 [18 months after the first interim analysis]) for the committee’s consideration. The second interim analysis includes an updated descriptive analysis of event-free survival and overall survival, a descriptive analysis of disease-free survival, updated exposure and safety data, and an analysis of patient reported outcomes and health-related quality of life in the adjuvant phase of the study.

These updated results confirm the positive benefit-risk profile of durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, as indicated for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) non-small cell lung cancer and no known epidermal growth factor receptor mutations or anaplastic lymphoma kinase rearrangements.

At the second interim analysis (data cutoff 10 May 2024):

<u>Event-free survival</u>
The event-free survival hazard ratio is 0.69 (95% confidence interval 0.55 to 0.88) which is consistent with the hazard ratio reported at the first interim analysis (data cutoff 10 November 2022). The median follow-up is 25.9 months and represent 39% event-free survival data maturity.

Importantly, the clear separation in the event-free survival Kaplan-Meier curves favouring the perioperative durvalumab arm that was observed from approximately 3 months post-randomisation at the first interim analysis has been maintained over time. This is demonstrated by the greater proportion of patients in the perioperative durvalumab arm who were alive and event-free at 12 months, 24 months, and 36 months post-randomisation compared to the perioperative placebo arm (see Additional evidence document Table 5 and Figure 1).

<u>Disease-free survival</u>
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	The second interim analysis shows a trend towards improved disease-free survival in favour of perioperative durvalumab over perioperative placebo, with a hazard ratio of 0.66 (95% confidence interval 0.47 to 0.92; p-value 0.013652). Per the AEGEAN statistical analysis plan, a p-value <0.012303 was required to declare statistical significance at the second interim analysis. However, the disease-free survival Kaplan-Meier curves show a clear and sustained separation from approximately 2 months post-surgery that favours the perioperative durvalumab (Additional evidence document Figure 2), as shown by a greater proportion of patients in the perioperative durvalumab arm who were alive and recurrence-free at 12 months, 24 months, and 36 months post-surgery compared to the perioperative placebo arm. Median disease-free survival was not reached in either treatment arm. **Overall survival** The company submission reported overall survival hazard ratios for two available data cuts: • At the first interim analysis (data cutoff 10 November 2022), in which overall survival data were 22.1% mature, the overall survival hazard ratio was 1.02 (95% confidence interval 0.75 to 1.39) • At the Day 120 Safety Update provided to the US Food and Drug Administration (data cutoff [redacted]), the observed hazard ratio had numerically improved to [redacted] (95% confidence interval [redacted] to [redacted]) to favour perioperative durvalumab over perioperative placebo At the second interim analysis (data cutoff 10 May 2024), an updated descriptive analysis of overall survival (35% data maturity) shows further numerical improvement in the hazard ratio to 0.89 (95% confidence interval 0.70 to 1.14), continuing the trend towards improved overall survival for perioperative durvalumab over perioperative placebo. Median overall survival was not reached for the perioperative durvalumab arm, compared to a median OS of 53.2 months in the perioperative placebo arm. Each subsequent data cut shows a clear separation between the perioperative durvalumab and perioperative placebo in the Kaplan-Meier curves. The observed overall survival trend and separation of the curves supports the plausibility of a further survival benefit emerging with longer term follow up. Event-free survival has been confirmed by the committee as the most relevant endpoint for decision making; the addition of disease-free survival results indicate that patients who can undergo the full perioperative treatment plan (i.e., neoadjuvant treatment and surgery followed by adjuvant treatment) can further benefit from protection from cancer recurrence. Overall, the additional evidence reported for the survival outcomes of event-free-, disease-free-, and overall survival in AEGEAN, reduces uncertainty and supports the survival benefit, alongside a reduced risk of recurrence after resection, for perioperative durvalumab over perioperative placebo. Perioperative durvalumab remains cost-effective at a £20,000 per QALY willingness-to-pay threshold using the second interim analysis data (ICER = £5,374).
3	**A matching-adjusted indirect comparison remains the most robust methodology to appropriately adjust for treatment-effect modifiers and inform decision making for perioperative durvalumab** **Summary** The committee noted that only one method of indirect treatment comparison had been presented for the comparison with neoadjuvant nivolumab and that the CheckMate 816

	population that the AEGEAN data were matched to via this method differed from UK clinical practice. This was contrary to the committee conclusions in TA876, where the committee concluded that the CheckMate 816 population was likely representative of the UK population and appropriate for decision making.[1] The committee requested that alternative indirect treatment comparison methods were used for the comparison of perioperative durvalumab and neoadjuvant nivolumab, such as multilevel network meta-regression. After further reassessment of the appropriate methods for comparison, the company maintain that a matching-adjusted indirect comparison is the most appropriate method for decision making. This approach is robust and thoroughly tested using sensitivity analyses. A population adjusted indirect comparison is required due to the differences in the effect modifiers across trials and using multilevel network meta-regression cannot appropriately adjust for treatment-effect modifiers. The results of the matching-adjusted indirect comparison analyses (constant and time-varying) are consistent with previous results and indicate that perioperative durvalumab remains a cost-effective treatment option versus neoadjuvant nivolumab, and other treatments (ICERs below £20,000 per QALY gained in all scenarios). The MAIC analyses and ML-NMR feasibility assessment are discussed further below. **Updated matching-adjusted indirect comparison analysis (second interim analysis)** As described in response to section 3.4 of the draft guidance document, in light of the differences in disease stage between CheckMate 816 and patients in UK clinical practice, the matching-adjusted indirect comparison of perioperative durvalumab versus neoadjuvant nivolumab is likely to provide a conservative estimate of the efficacy of perioperative durvalumab expected in the patient population seen in UK clinical practice. The matching-adjusted indirect comparison for perioperative durvalumab versus neoadjuvant nivolumab has been updated with data from the second interim analysis (data cutoff 10 May 2024) for AEGEAN. The results are presented in the additional evidence document section 1.2. Similar trends (versus first interim analysis event-free survival results) are seen with the updated analyses. In the 3+ month time interval, which is when the majority of events occurred in each trial, the base case event-free survival hazard ratio for perioperative durvalumab versus neoadjuvant nivolumab + platinum chemotherapy was [redacted] (95% confidence interval [redacted] to [redacted]). The network meta-analyses of perioperative durvalumab compared with adjuvant chemotherapy and surgery only have also been updated with the latest AEGEAN data, for completeness. The results are presented in the Additional Evidence Document section 1.3 and were also consistent with those previously reported in the original submission. The preferred analysis (piecewise sensitivity analysis 2) resulted in a random effects event-free survival hazard ratio for the 3+ month time interval of [redacted] (95% confidence interval [redacted] to [redacted]) versus adjuvant chemo and [redacted] (95% confidence interval [redacted] to [redacted] versus surgery. **Multilevel network meta regression feasibility assessment** After receiving the draft guidance, the company conducted a feasibility assessment for a multilevel network meta-regression analysis. As per the EAG clarification question A22, a multilevel network meta-regression was considered in which all relevant comparators (i.e.

	neoadjuvant nivolumab, adjuvant chemotherapy, surgery only and neoadjuvant chemotherapy) were included in the network. The network for the multilevel network meta-regression therefore included those trials in the preferred network for the NMA (AEGEAN, NATCH, CHEST, MRC LU22/NVALT 2/EORTC 08012, and SWOG S9900), as well as CheckMate-816. Limited reporting of baseline characteristics which were considered possible effect modifiers (i.e. smoking status and PD-L1 expression) across trials (for adjuvant chemotherapy and surgery) was noted. There were also differences in staging systems and reported stage (by TNM or stage II/III) in these trials making it challenging to assess and adjust for differences between trials in disease stage. For example, staging system was only reported for the CHEST trial (5th edition, compared to the 7th edition used in CheckMate-816 and 8th edition used in AEGEAN), and not reported in the three other adjuvant chemotherapy/surgery trials in the network. The covariates which would have been included in the multilevel network meta-regression would therefore have been restricted to baseline characteristics available across all studies (sex, region, planned platinum chemotherapy and histology). This limitation was originally concluded in the company response to EAG clarification question A22, in which the EAG requested a multilevel network meta-regression. Only including these baseline characteristics, and not other potential effect modifiers (such as disease stage, PD-L1 expression and smoking status), would therefore be a substantial limitation of the multi-level network meta-regression, which would result in highly uncertain results. Age was not included as a covariate in the matching-adjusted indirect comparison and would not be included in the multilevel network meta-regression, as this is not a known or expected treatment-effect modifier. Adjusting for age is not expected to have a major impact on relative efficacy estimates in the indirect treatment comparisons (refer to Comment 2). A key feature of multi-level network meta-regression is the ability to model treatment effect modification for all treatments in the network (i.e. population adjustment is carried out for all treatments). In doing so, multi-level network meta-regression can generate estimates of relative efficacy within any specified patient population. According to Phillippo 2020, the data requirements for estimating a treatment effect and independent effect modifier interaction for a given treatment *k* are either: • Individual patient data from one or more trials including treatment *k* or • Sufficiently many aggregate data studies including treatment *k*, with enough variation in covariate values (of note, in Phillippo 2023, five studies of aggregate data for a given treatment was considered to be insufficient) Importantly, neither of the above criteria were satisfied for any of the other interventions: neoadjuvant nivolumab (one aggregate study), adjuvant chemotherapy (one aggregate study) or surgery (four aggregate studies). Therefore, the shared effect modifier assumption would need to be applied to all treatments included in a multilevel network meta-regression (perioperative durvalumab, neoadjuvant nivolumab, surgery, adjuvant chemotherapy). This borrows information of effect modification from the individual patient data trial (i.e. from AEGEAN) and assumes this effect is shared across all other treatments within the treatment set. The shared effect modifier assumption in this network is fundamental for conducting a robust multi-level network meta-regression. Following an assessment of the available data for the studies in the network, the analysis was deemed implausible for the following reasons:

- There is heterogeneity of effect modifiers. For example, there are differences in treatment class (surgery only; chemotherapy plus surgery; immunotherapy plus chemotherapy and surgery) and treatment approaches (neoadjuvant only; adjuvant only; perioperative) within the network. This heterogeneity can lead to biased estimates if the assumption is not met.

- Despite belonging to the same treatment class, it is not appropriate to assume the same effect modification between (perioperative) durvalumab and (neoadjuvant only) nivolumab, which are distinct treatment regimens. Contrary to the shared effect modifier assumption, the event-free survival subgroup analyses from AEGEAN and CheckMate-816 indicate that effect modification is not the same for perioperative durvalumab and neoadjuvant nivolumab. For example, in AEGEAN, event-free survival hazard ratios versus neoadjuvant chemotherapy were largely consistent across PD-L1 subgroups (<1% and ≥1%) and histology subgroups (non-squamous and squamous), but larger differences between these subgroups were evident in the CheckMate-816 trial. Furthermore, in certain subgroups the direction of effect modification was different in each trial, e.g. in AEGEAN, a lower event-free survival hazard ratios was reported in the planned cisplatin subgroup (planned platinum chemotherapy) and in males (gender). Whereas in CheckMate-816, a lower event-free survival hazard ratio was reported in the carboplatin subgroup and in females.

- Due to the sparse information available, with individual patient data available from the AEGEAN trial only, and with information for neoadjuvant nivolumab and adjuvant chemotherapy available from a single aggregate trial each (CheckMate-816 and NATCH, respectively), it is also not possible to test (i.e. with adequate power) the validity of the shared effect modifier assumption in this network using the methods described in Phillippo et al. 2023. Multilevel network meta-regression provides a powerful tool for population-adjustment treatment comparisons. However, in this instance it is reliant on the strong assumption of shared effect modification, which is invalid for this network due to the clinical implausibility of the assumption (varying treatment classes and regimens).

Given the above limitations, it was not feasible to conduct a robust multilevel network meta-regression and this method was considered inappropriate to inform the comparative efficacy of durvalumab and relevant comparators. In order therefore to address the Committee's feedback, and further explore uncertainty related to the matching-adjusted indirect comparison, additional sensitivity analyses were conducted.

Matching-adjusted indirect comparison scenario analyses

As stated in the company submission, the matching-adjusted indirect comparison is preferred as it enables adjustment for expected treatment-effect modifiers. Compared with the multilevel network meta-regression, additional expected treatment-effect modifiers (smoking status, PD-L1 expression and disease stage) can be adjusted for in the matching-adjusted indirect comparison and therefore, remains the preferred approach for indirect comparison.

The committee discussed the appropriateness of assuming proportional hazards between perioperative durvalumab and neoadjuvant nivolumab over the model's lifetime. To address the committee's query, and to investigate further uncertainty regarding the matching-adjusted

	indirect comparison, the application of time-varying hazard ratios was explored to relax the assumption of proportional hazards. This involved deriving time-varying event-free survival hazard ratios for perioperative durvalumab and neoadjuvant nivolumab versus neoadjuvant platinum doublet chemotherapy, following the methodology reported by Cope 2020 (multivariate network-meta analysis of survival parameters),[2] as referenced by the EAG in clarification question A24. See full methodology details in section 1.5 of the additional evidence document. To identify the most suitable survival curve that fits the observed survival data from each of the studies, methods from the DSU guidance were followed, including assessment of statistical fit, visual fit, and long-term plausibility. Based on the AIC statistics (see Table 17 in the Additional Evidence Document), the Gompertz distribution showed the best statistical fit for all treatment arms (except for neoadjuvant nivolumab), while the log-normal distribution presented the best statistical fit for neoadjuvant nivolumab and second best for all other treatments arms. Based on the model fits (see Figure 11 in the additional evidence document), all distributions have a good visual fit to the Kaplan-Meier curves for both AEGEAN[3] and CheckMate 816.[4] However, due to clinically implausible event-free survival hazard ratios in the longer term (see Figure 12 in the Additional Evidence Document), the Gompertz curve was not considered the most clinically plausible. The log-normal distribution, being the second-best fitting statistically, showed clinically plausible event-free survival hazard ratios over time and was therefore selected as the most appropriate curve. Moreover, the log-normal distribution aligned with the distribution used in TA876,[1] and the company submission base case for the piecewise extrapolation of perioperative placebo event-free survival. The analysis of the time-varying hazard ratio approach using the log-normal base case indicates that the event-free survival hazard ratio for perioperative durvalumab compared to neoadjuvant nivolumab decreases over time to approximately [redacted] and stabilises after 6 months post-randomisation. In contrast, the constant hazard ratio from the piecewise matching-adjusted indirect comparison for the period beyond 3 months is [redacted]. Therefore, the cost-effectiveness results of the piecewise constant event-free survival hazard ratios used in the company submission were more conservative, favouring perioperative durvalumab less, than the results from the time-varying event-free survival hazard ratios using the log-normal base case (see Table 49 in the additional evidence document). Additionally, the time-varying hazard ratio approach demonstrates that the proportional hazards assumption is violated in the first few months but holds afterwards (see Figure 13 in the additional evidence document). This finding supports the use of the piecewise approach in the company submission. Perioperative durvalumab remains cost-effective at a £20,000 per QALY willingness-to-pay threshold using constant and time-varying matching-adjusted indirect comparison approaches (ICER = £5,374 and perioperative durvalumab dominates, respectively), validating the robustness of the matching-adjusted indirect comparison for decision making.
4	**Age of diagnosis for patients undergoing resection is not an effect modifier but is expected to be consistent with the AEGEAN study in UK clinical practice**

	The company disagree with the committee's conclusion that there were some key differences between the AEGEAN and CheckMate 816 trials and UK clinical practice (such as disease stage and age) that would need to be accounted for in the indirect treatment comparison and the modelling. The most recent National Lung Cancer Audit (published 2024 for the year 2022) reports a median age of 74 years at diagnosis.[5] We agree with the clinical expert consulted by the committee in that patients that undergo resection for non-small cell lung cancer in UK clinical practice would be younger than the median age of diagnosis of non-small lung cancer in the UK (74 years). However, the median age of diagnosis does not specifically represent the early stage, resectable population, but rather a much broader group of non-small cell lung cancer being diagnosed in the UK. Clinical validation confirmed that the age of the AEGEAN trial population was generalisable to UK clinical practice.[6] Differences in the age of patients that are expected to receive perioperative durvalumab are not expected to have an impact on the survival outcomes observed in AEGEAN, and as such it is not necessary to consider age as a treatment effect modifier and further account for age in the indirect treatment comparison or economic modelling. Subgroup analyses for event-free survival in AEGEAN at the first (data cutoff 10 November 2022) and second (data cutoff 10 May 2024) interim analyses demonstrate there is consistent benefit between the overall modified intent-to-treat population and either patients aged <65 years or ≥65 years. Upon visual inspection of the forest plots, the 95% confidence intervals for each age subgroup and the modified intent-to-treat population overlap with one another. Furthermore, in AEGEAN,[7] a post-hoc sensitivity analysis was conducted to assess the consistency of event-free survival treatment effect across age subgroups using interaction tests. Tests for effect modification were conducted by comparing models with and without the interaction term (i.e., treatment + covariate + treatment * covariate interaction vs treatment + covariate) using likelihood ratio tests. There was no significant interaction (5% significance level) between treatment group and the baseline subgroup variable of age for event-free survival in AEGEAN subgroup interaction tests (post-hoc analysis); this result is expected as age is not a known or expected effect modifier of treatments in early-stage lung cancer Thus, the company maintain that the company base case is appropriate for decision making.
5	**Disease stage is an expected treatment-effect modifier and when adjusted for, alongside other expected treatment-effect modifiers, shows a survival benefit of perioperative durvalumab compared with neoadjuvant nivolumab in the matching-adjusted indirect comparison** The committee noted that there was variation in proportions of different disease stages at diagnosis between the two clinical trials and the proportions in the National Lung Cancer Audit (NLCA) 2024 report.[5] We note that the NLCA 2024 reports percentages for disease stage at diagnosis for all patients diagnosed with lung cancer in England during 2022 and does not report disease stage for the sub-population of patients with non-small cell lung cancer eligible for resection specifically.[8] AEGEAN includes patients with resectable non-small cell lung cancer with stage IIA to IIIB disease only[9] and the proportion of patients in each disease stage is consistent with UK clinical practice as reported by the NLCA 2024. For all patients with lung cancer, approximately 25% are diagnosed with stage I, 8% with stage II, 12% with stage IIIA, 9% with stage IIIB, and 45% with stage IV lung cancer.[5] In clinical practice, there are 2.5 times more patients diagnosed with

	stage III than stage II lung cancer. In AEGEAN, there were also 2.5 times more patients with stage III (71%) than stage II disease (29%), a similar proportion to what is seen in UK clinical practice. CheckMate 816 included 64% with stage IIIA and 35% with stage IB or II.[10] That is, a smaller proportion of patients had stage III disease compared with UK clinical practice. However, in TA876, the Appraisal Committee did not consider disease stage to be a generalisability concern and concluded that the trial population of CheckMate 816 was likely representative of UK clinical practice and thus appropriate for decision making.[1] As shown in subgroup analyses of both AEGEAN and CheckMate 816, disease stage is likely to be a treatment effect modifier, which a greater improvement in event-free survival with neoadjuvant nivolumab or perioperative durvalumab for patients with stage III disease compared with patients with stage I or II.[9,10] As disease stage is a potential treatment effect modifier it was adjusted for in the base case matching-adjusted indirect comparison together with all other potential treatment effect modifiers. Only adjusting the AEGEAN data to match the CheckMate 816 data for disease stage would lead to a smaller proportion of patients with disease stage III, which would likely lead to a decrease in the relative benefit of perioperative durvalumab compared with neoadjuvant nivolumab in the overall population. Consistent with DSU guidance, all potential treatment effect modifiers were adjusted for in the base case, leading to an overall increased benefit of perioperative durvalumab versus neoadjuvant nivolumab. The difference in disease stage between CheckMate 816 and patients seen in UK clinical practice, with fewer patients with stage III disease, where the greatest relative benefit of treatment is expected, means that the matching-adjusted indirect comparison hazard ratios are likely to be conservative relative to UK clinical practice.
6	**The company has reported all relevant outcomes** There is a factual inaccuracy in section 3.5 of the draft scope. The text states that disease-free survival, adverse events and health-related quality of life data had not been reported. Adverse event and health related quality of life data were reported in the company submission and additional health-related quality of life outcomes were reported in the at clarification. The company agree with the committee that event-free survival is the most relevant outcome for this appraisal. As described in comments relating to section 3.3 above, updated event-free survival results from the second interim analysis have been provided by the company for the committee's consideration. Disease-free survival is also available from this data-cut and has been provided as supportive evidence.
7	**Based on clinical expert opinion, 95% of non-small cell lung cancer patients who are event-free at 5 years should be considered cured** Despite uncertainty, the committee found it likely appropriate to model a cure assumption but recommended the company provide scenarios with varying time points, cure proportions, and without a cure assumption. The concept of a functional cure is well established in this disease setting and should inform clinical management. While identified as an area of uncertainty, there is strong precedent for

	capturing cure in early-stage non-small cell lung cancer (TA761, TA823, TA876),[1,11-13] where clinical experts agree that patients who remain event- or disease-free after five years are functionally cured. Across these submissions, the committee found a cure assumption reasonable, despite uncertainties around the exact cure timepoint and proportion of patients cured. As detailed in the company submission, an advisory board of five UK clinical experts extensively validated the cure timepoint for perioperative durvalumab. All clinicians agreed on the plausibility of a cure, with three advisors supporting the five-year cure timepoint based on current evidence. One advisor noted that around 2% of patients might recur after five years, making it reasonable to assume that less than 5% of patients alive and event-free at five years may not be cured (per the company submission base case). In addition, a targeted literature review on non-small cell lung cancer cure assumptions showed that recurrence risk significantly decreases five years post-surgery, with only a few patients experiencing recurrence beyond this point, as described in Section B.3.3.3.3 of the company submission. The company base case captures this clinical insight by applying the same 5-yearscure timepoint and 95% proportion for perioperative durvalumab and neoadjuvant nivolumab. In response to the committee's request, scenario analyses were conducted to assess the impact of conservative cure assumptions: 1) a 6-year cure timepoint and 2) no cure applied. The results show that perioperative durvalumab remains cost-effective at a £20,000 per QALY willingness-to-pay for each scenario (Section 2.4.2.3 of the Additional Evidence Document). In summary, the company's base case approach appropriately captures the long-term curative potential of perioperative durvalumab by extending event-free survival post-resection, and is consistent with NICE committee assumptions across previous appraisals in early-stage lung cancer.
	References: 1. National Institute for Health and Care Excellence (NICE). *Nivolumab with chemotherapy for neoadjuvant treatment of resectable non small-cell lung cancer (TA876)*. 2023. https://www.nice.org.uk/guidance/ta876 2. Cope S, Chan K, Jansen JP. Multivariate network meta-analysis of survival function parameters. *Res Synth Methods*. May 2020;11(3):443-456. doi:10.1002/jrsm.1405 3. AstraZeneca. *Oncologics Drugs Advisory Committee (ODAC) Meeting July 25, 2024. Addendum to the Combined FDA and Applicant ODAC briefing Document.* 2024. Accessed August 20, 2024. https://www.fda.gov/advisory-committees/updated-agenda-information-july-25-2024-meeting-oncologic-drugs-advisory-committee-meeting 4. Spicer J, Girard N, Provencio M, et al. Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816 *J Clin Oncol*. 2024;42(suppl 17; abstr LB8010)doi:10.1200/JCO.2024.42.17_suppl.LBA8010 5. Royal College of Physicians. *National Lung Cancer Audit: State of the Nation Report 2024*. 2024. https://www.lungcanceraudit.org.uk/wp-content/uploads/2024/05/NLCA-State-of-the-Nation-2024_16.05.24_V2.0.pdf

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 20 August 2024. Please submit via NICE Docs.

	6. AstraZeneca Lung Cancer Global/UK Advisory Board. *Early Stage Resectable Non-Small Cell Lung Cancer Advisory Board (AEGEAN). 19th January 2024, virtual meeting. 2024.* 2024. 7. AstraZeneca. *A Phase III, Double-blind, Placebo-controlled, Multi-center International Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients with Resectable Stages II and III Non-small Cell Lung Cancer (AEGEAN): Clinical Study Report*. 2023. 8. National Institute for Health and Care Excellence (NICE). *Lung cancer: diagnosis and management. NICE guideline [NG122]*. 2023. https://www.nice.org.uk/guidance/ng122 9. Heymach JV, Harpole D, Mitsudomi T, et al. Perioperative Durvalumab for Resectable Non-Small-Cell Lung Cancer. *N Engl J Med*. Nov 2 2023;389(18):1672-1684. doi:10.1056/NEJMoa2304875 10. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. May 26 2022;386(21):1973-1985. doi:10.1056/NEJMoa2202170 11. Ades AE, Mavranezouli I, Dias S, Welton NJ, Whittington C, Kendall T. Network meta-analysis with competing risk outcomes. *Value Health*. Dec 2010;13(8):976-83. doi:10.1111/j.1524-4733.2010.00784.x 12. National Institute for Health and Care Excellence (NICE). Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (TA761). *Available at: https://wwwniceorguk/guidance/ta761 [Accessed September 2023]*. 2022; 13. National Institute for Health and Care Excellence (NICE). *Atezolizumab for adjuvant treatment of resected nonsmall-cell lung cancer (TA823)*. 2022. https://www.nice.org.uk/guidance/ta823

Insert extra rows as needed

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Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]

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Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]

Draft guidance consultation – Additional evidence

The purpose of this document is to provide additional data and analyses requested by the committee in the draft guidance document. These include:

- Updated efficacy and safety results from the second interim analysis of the AEGEAN study (IA2), corresponding to a data cut-off (DCO) date of 10 May 2024[1]
- An updated matching-adjusted indirect comparison (MAIC) and network-meta analysis (NMA) using AEGEAN IA2 data
- A cost-effectiveness scenario analysis applying time-varying hazard ratios (HRs) across the entire trial period.

1 Additional Clinical Evidence

1.1 AEGEAN Trial Interim Analysis 2 Results

The IA2 data (DCO 10 May 2024) reported below include an updated descriptive analysis of EFS and OS, a descriptive analysis of DFS, updated exposure and safety data, and an analysis of patient-reported outcomes and health-related quality of life in the adjuvant phase of the study. These updated results confirm the positive benefit-risk profile of durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, as indicated for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.

1.1.1 Patient Disposition

At IA2, all patients in both treatment arms had completed adjuvant treatment and the safety follow-up period. Of those patients who started adjuvant treatment (242 patients in the perioperative durvalumab arm and 237 patients in the placebo arm), 166 patients (68.6%) in the perioperative durvalumab and 151 patients (63.7%) in the placebo arm completed all 12 planned cycles of adjuvant treatment. Radiological progression according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 continued to be the most common reason for discontinuation of adjuvant treatment in both treatment arms (30/242 patients [12.4%] for the perioperative durvalumab arm and 59/237 patients [24.9%] for the placebo).

The subset of the modified intent-to-treat (mITT) population used for evaluation of the key secondary endpoint of DFS and adjuvant period patient-reported outcomes (PROs) is known

as the modified resected set (mRS) in the study protocol. For simplicity, in this document, it is hereafter referred to as “resected mITT population”. This analysis set comprised patients in the mITT population who had received neoadjuvant treatment, completed surgical resection, and whose first post-surgical RECIST scan showed no disease, and excluded patients with R2 resection margins.

At IA2, a total of 473 randomized patients were included in the resected mITT population: 242 patients in the perioperative durvalumab arm and 231 patients in the placebo (Table 1). Adjuvant durvalumab/placebo treatment was started by 223 patients (92.1%) in the perioperative durvalumab arm and 214 patients (92.6%) in the perioperative durvalumab arm; among these patients, all 12 cycles of adjuvant durvalumab/placebo were completed by 158 patients (70.9%) in the perioperative durvalumab arm and 139 patients (65.0%) in the placebo arm.

Table 1. Patient disposition at AEGEAN IA2, mITT and resected mITT populations

Study phase	Participants, n (%)			
	mITT population		Resected mITT population	
	Perioperative durvalumab (n=366)	Perioperative placebo (n=374)	Perioperative durvalumab (n=242)	Perioperative placebo (n=231)
Neoadjuvant, n (%)				
Randomised	366 (100)	374 (100)	242 (100)	231 (100)
Received treatment	366 (100)	371 (99.2)	242 (100)	231 (100)
Completed 4 cycles of both chemotherapy agents	310 (84.7)	326 (87.2)	217 (89.7)	215 (93.1)
Completed 4 cycles of durvalumab/placebo	318 (86.9)	331 (88.5)	222 (91.7)	220 (95.2)
Surgery, n (%)				
Underwent surgery[a]	295 (80.6)	302 (80.7)	242 (100)	231 (100)
Completed surgery	284 (77.6)	287 (76.7)	242 (100)	231 (100)
Adjuvant, n (%)				
Started durvalumab/placebo[b]	242 (66.1)	237 (63.4)	223 (92.1)	214 (92.6)
Completed durvalumab/placebo	166 (45.4)	151 (40.4)	158 (65.3)	139 (60.2)
Discontinued durvalumab/placebo	76 (20.8)	86 (23.0)	65 (26.9)	75 (32.5)
Ongoing durvalumab/placebo	0	0	0	0

DCO 10 May 2024

Abbreviations: DCO, data cut-off; mITT, modified intent-to-treat; RECIST, Response Evaluation Criteria in Solid Tumours

[a] Excludes patients with surgery done outside of the study.

[b] Includes 3 patients who did not complete surgery in the mITT population (1 participant in the perioperative durvalumab group and 2 participants in the perioperative placebo group).

Source: AstraZeneca 2024[1]

1.1.2 Demographics and Baseline Characteristics in the Resected mITT Population

Overall, demographics and baseline disease characteristics of patients in the resected mITT population were generally similar to those in the mITT population. Within the resected mITT population, both patient (Table 2) and disease (Table 3) characteristics were generally well balanced across the two treatment arms. Overall, imbalances between treatment arms were minor (<10%).

Table 2. Key patient demographics and baseline characteristics at AEGEAN IA2, mITT and resected mITT populations

Characteristic	Participants, n (%)			
	mITT population		Resected mITT population	
	Perioperative durvalumab (n=366)	Perioperative placebo (n=374)	Perioperative durvalumab (n=242)	Perioperative placebo (n=231)
Median age, years (range)	65 (30–88)	65 (39–85)	65 (32-88)	64 (40-85)
≥75 years, n (%)	44 (12.0)	36 (9.6)	29 (12.0)	28 (12.1)
Male, n (%)	252 (68.9)	278 (74.3)	161 (66.5)	167 (72.3)
Race, n (%)				
Asian	143 (39.1)	164 (43.9)	99 (40.9)	111 (48.1)
White	206 (56.3)	191 (51.1)	155 (55)	107 (46.3)
Other	17 (4.6)	19 (5.1)	10 (4.1)	13 (5.6)
Region, n (%)				
Asia	142 (38.8)	163 (43.6)	98 (40.5)	111 (48.1)
Europe	141 (38.5)	140 (37.4)	98 (40.5)	76 (32.9)
North America	43 (11.7)	43 (11.5)	24 (9.9)	26 (11.3)
South America	40 (10.9)	28 (7.5)	22 (9.1)	18 (7.8)
Smoking status, n (%)				
Never	51 (13.9)	56 (15.0)	38 (15.7)	43 (18.6)
Former	220 (60.1)	223 (59.6)	137 (56.6)	140 (60.6)
Current	95 (26.0)	95 (25.4)	67 (27.7)	48 (20.8)

DCO 10 May 2024

Abbreviations: DCO, data cut-off; mITT, modified intent-to-treat
Source: AstraZeneca 2024[1]

Table 3. Key disease characteristics at AEGEAN IA2, mITT and resected mITT populations

Characteristic	Participants, n (%)			
	mITT population		Resected mITT population	
	Perioperative durvalumab (n=366)	Perioperative placebo (n=374)	Perioperative durvalumab (n=242)	Perioperative placebo (n=231)
ECOG performance status, n (%)				
0	251 (68.6)	255 (68.2)	182 (75.2)	162 (70.1)
1	115 (31.4)	119 (31.8)	60 (24.8)	69 (29.9)
AJCC stage[a] at diagnosis, n (%)				
II	104 (28.4)	110 (29.4)	76 (31.4)	79 (34.2)
IIIA	173 (47.3)	165 (44.1)	114 (47.1)	96 (41.6)
IIIB	88 (24.0)	98 (26.2)	52 (21.5)	55 (23.8)
Histology type, n (%)				
Squamous	169 (46.2)	191 (51.1)	107 (44.2)	113 (48.9)
Non-squamous	196 (53.6)	179 (47.9)	134 (55.4)	117 (50.6)
TNM classification				
Primary tumour, n (%)				
T1	44 (12.0)	43 (11.5)	29 (12.0)	21 (9.1)
T2	97 (26.5)	108 (28.9)	66 (27.3)	70 (30.3)
T3	128 (35.0)	129 (34.5)	85 (35.1)	89 (38.5)
T4	97 (26.5)	94 (25.1)	62 (25.6)	51 (22.1)
Regional lymph nodes, n (%)				
N0	110 (30.1)	102 (27.3)	80 (33.1)	64 (27.7)
N1	75 (20.5)	87 (23.3)	51 (21.1)	67 (29.0)
N2	181 (49.5)	185 (49.5)	111 (45.9)	100 (43.3)
PD-L1 expression, n (%)				
TC <1%	122 (33.3)	125 (33.4)	72 (29.8)	79 (34.1)
TC 1-49%	135 (36.9)	142 (38.0)	90 (37.2)	86 (37.2)
TC ≥50%	109 (29.8)	107 (28.6)	80 (33.1)	66 (28.6)
Planned neoadjuvant platinum agent, n (%)				
Cisplatin	100 (27.3)	96 (25.7)	72 (29.8)	60 (26.0)
Carboplatin	266 (72.7)	278 (74.3)	170 (70.2)	171 (74.0)

DCO 10 May 2024

Abbreviations: AJCC, American Joint Committee on Cancer; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; PD-L1, programmed cell death ligand-1; TNM, tumour-node-metastasis

[a] AJCC 8th edition[2]

Source: AstraZeneca 2024[1]

1.1.3 Anti-cancer Therapy Post-Treatment Discontinuation

At IA2, in the mITT population, subsequent anti-cancer therapy was received by 19.4% of patients in the perioperative durvalumab arm and 29.7% of patients in the perioperative placebo arm (Table 4). Systemic therapies were most frequently cytotoxic chemotherapy (12.8% of patients in the perioperative durvalumab arm and 13.6% of patients in the perioperative placebo arm) and immunotherapy-based regimens (7.1% and 16.8% of patients, by respective treatment arm). Radiotherapy (as a subsequent therapy) was received by 12.0% of patients in the perioperative durvalumab and 17.6% of patients in the perioperative placebo arm, including concomitant chemoradiotherapy (6.0% and 5.3% of patients, respectively).

Table 4. Subsequent anti-cancer therapy at AEGEAN IA2, mITT population

Anti-cancer therapy regimen[a]	Perioperative durvalumab (n=366)	Perioperative placebo (n=374)
Post-discontinuation anti-cancer therapy, n (%)	**71 (19.4)**	**111 (29.7)**
Systemic therapy	70 (19.1)	111 (29.7)
Cytotoxic chemotherapy	47 (12.8)	51 (13.6)
Immunotherapy	26 (7.1)	63 (16.8)
Targeted therapy	7 (1.9)	8 (2.1)
Other	2 (0.5)	6 (1.6)
Radiotherapy	44 (12.0)	8 (2.1)
Concomitant chemoradiotherapy	22 (6.0)	6 (1.6)
Line of subsequent therapy		
1st	71 (19.4)	111 (29.7)
2nd	19 (5.2)	26 (7.0)
≥3rd	6 (1.6)	6 (1.6)
Intent of subsequent therapy		
Neoadjuvant	4 (1.1)	4 (1.1)
Adjuvant	7 (1.9)	13 (3.5)
Definitive	9 (2.5)	5 (1.3)
Maintenance	10 (2.7)	6 (1.6)
Palliative	53 (14.5)	87 (23.3)
N/A	1 (0.3)	0

DCO 10 May 2024
Abbreviations: DCO, data cut-off; mITT, modified intent-to-treat
Source: AstraZeneca 2024[1]

1.1.4 Event-Free Survival

At IA2 (approximately 18 months after the first interim analysis of AEGEAN [IA1]), an updated descriptive analysis of event-free survival (EFS; assessed by blinded independent central review [BICR] per RECIST 1.1) was conducted with an overall EFS data maturity of 39%. This included 53 new EFS events in the mITT population, for a total of 289 EFS events: 26 new EFS events in the perioperative durvalumab arm and 27 new EFS events in the perioperative placebo arm (Table 5). The median duration of follow-up in censored patients increased from

11.7 months at IA1 to 25.9 months at IA2. Overall, the majority of EFS events in both treatment arms were due to RECIST recurrence after surgery: 53 patients (14.5%) in the perioperative durvalumab arm vs. 83 patients (22.2%) in the perioperative placebo arm.

At IA2, the EFS HR was 0.69 (95% confidence interval [CI] 0.55 to 0.88), which is consistent with IA1 results, despite improved performance of the perioperative placebo arm (reflected in increased median EFS from 25.9 months at IA1 to 30.0 months at IA2). Median EFS was not reached for the perioperative durvalumab arm (Table 5). The separation in the EFS Kaplan-Meier (KM) curves favoring the perioperative durvalumab arm, which was observed from approximately 3 months post-randomization, was maintained over time, as shown by the greater proportions of patients in the perioperative durvalumab arm who were alive and event-free at 12 months, 24 months, and 36 months post-randomization compared to the perioperative placebo arm (Figure 1).

Subgroup analyses showed improvement in EFS favoring the perioperative durvalumab arm was maintained across all pre-specific subgroups at IA2, including race, age, geographic region, disease stage, programmed cell death ligand-1 (PD-L1) tumor cell (TC) expression status, and platinum chemotherapy agent. The robustness of the treatment effect was also demonstrated by the results of the EFS sensitivity analyses, which remained consistent with the main EFS analysis at IA2.

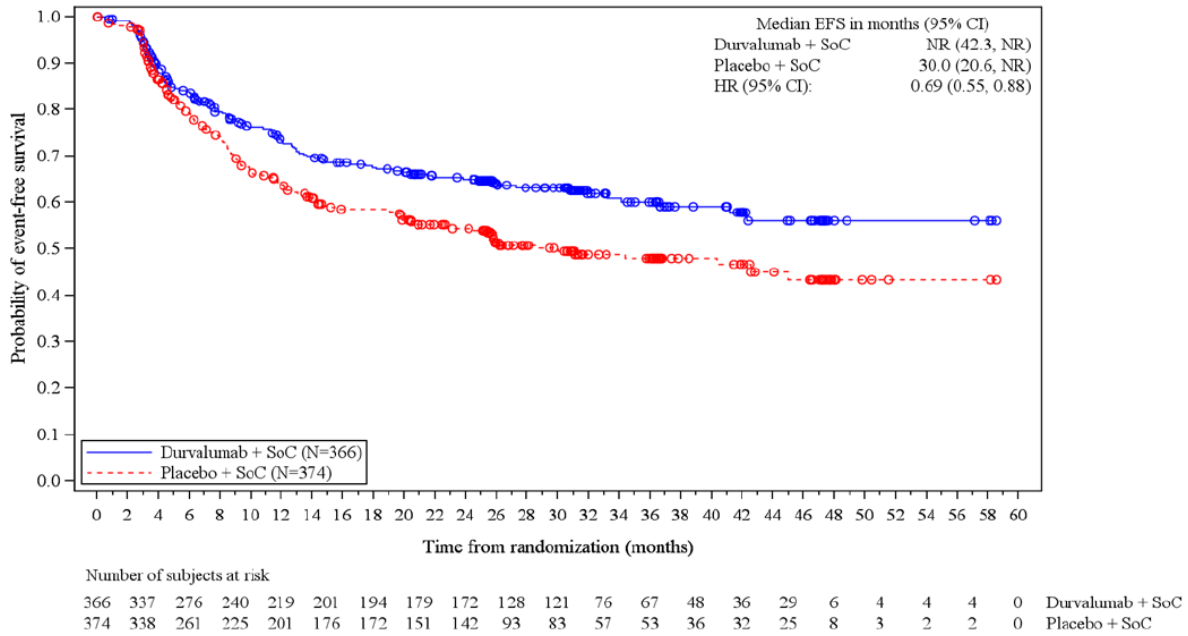
Table 5. Event-free survival assessed by BICR per RECIST 1.1 at AEGEAN IA1 and IA2, mITT population

	IA1 (DCO 10 Nov 2022)		**IA2 (DCO 10 May 2024)**	
	Perioperative durvalumab (n=366)	**Perioperative placebo (n=374)**	**Perioperative durvalumab (n=366)**	**Perioperative placebo (n=374)**
Events, n (%)	98 (26.8)	138 (36.9)	124 (33.9)	165 (44.1)
Progression that precluded surgery	26 (7.1)	35 (9.4%)	28 (7.7)	36 (9.6)
Progression discovered upon attempting surgery	5 (1.4)	13 (3.5)	5 (1.4)	13 (3.5)
RECIST recurrence after surgery	38 (10.4)	60 (16.0)	53 (14.5)	83 (22.2)
Death due to any cause	29 (7.9)	30 (8.0)	38 (10.4)	33 (8.8)
Censored patients, n (%)	268 (73.2)	236 (63.1)	242 (66.1)	209 (55.9)
Median EFS, months (95% CI)[a]	NR (31.9-NR)	25.9 (18.9-NR)	NR (42.3-NR)	30.0 (20.6-NR)
EFS at 12 months, % (95% CI)	73.4 (67.9-78.1)	64.5 (58.8-69.6)	73.3 (68.1-77.7)	64.1 (58.7-69.0)
EFS at 24 months, % (95% CI)	63.3 (56.1-69.6)	52.4 (45.4-59.0)	65.0 (59.4-70.0)	54.4 (48.7-59.6)
EFS at 36 months, % (95% CI)	NR	NR	60.1 (53.9-65.8)	47.9 (41.8-53.8)
HR (95% CI)	0.68 (0.53-0.88)		0.69 (0.55-0.88)	
2-sided p-value	0.003902		Formally analysed at IA2	

Abbreviations: EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumours

[a] Calculated using the Kaplan-Meier technique.
Source: AstraZeneca 2024[1]

Figure 1. Kaplan-Meier plot of event-free survival assessed by BICR per RECIST 1.1 at AEGEAN IA2, mITT population



DCO 10 May 2024
Note: Durvalumab and placebo refer to the perioperative durvalumab and the perioperative placebo arms in AEGEAN. Circles indicate censored observations.
Abbreviations: CI, confidence interval; DCO, data cut-off; EFS, event-free survival; mITT, modified intention to treat; NR, not reached
Source: AstraZeneca 2024[1]

1.1.5 Disease-Free Survival

At IA2, based on an overall disease-free survival (DFS) data maturity of 30%, DFS results were not statistically significant. Results indicate a trend toward improved DFS in favor of the perioperative durvalumab arm compared to the perioperative placebo arm, with a HR of 0.66 (95% CI 0.47 to 0.92; p-value 0.013652). A p-value <0.012303 was required to declare statistical significance at this interim analysis. Median DFS was not reached for either treatment arm (Table 6).

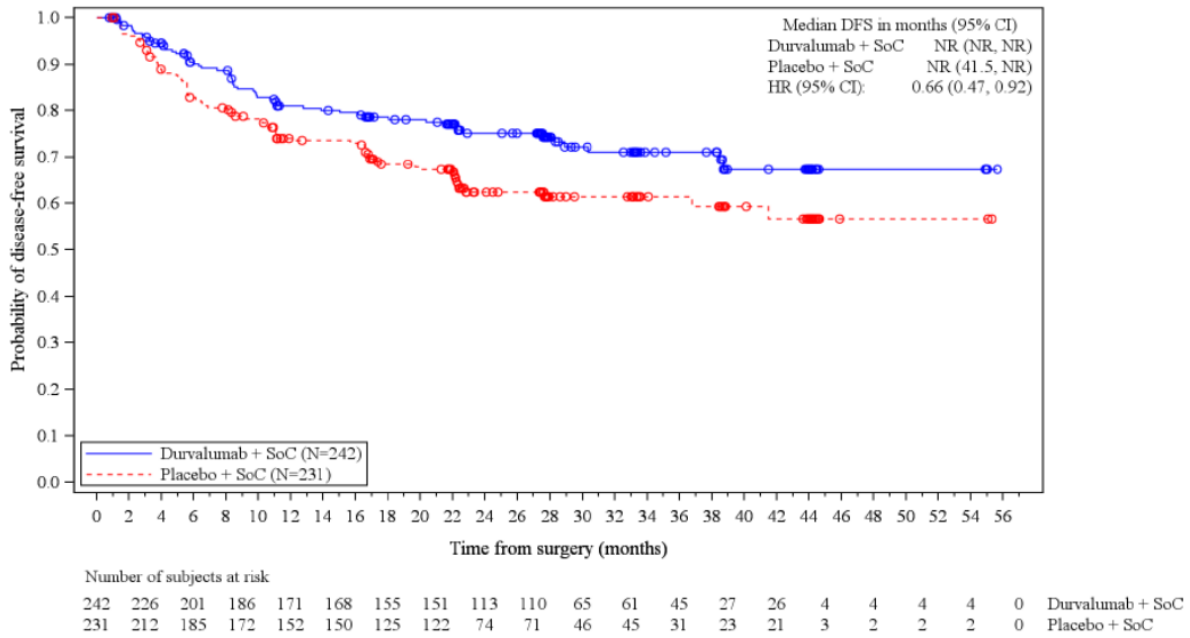
The DFS Kaplan-Meier curves overlapped until approximately 2 months post-surgery, after which there was a clear and sustained separation that favored the perioperative durvalumab arm (Figure 2), as shown by a greater proportion of patients in the perioperative durvalumab arm who were alive and recurrence-free at 12 months, 24 months, and 36 months post-surgery compared to the perioperative placebo arm (Table 6).

Table 6. Disease-free survival assessed by BICR per RECIST 1.1 at AEGEAN IA2, resected mITT population

	Perioperative durvalumab (n=242)	Perioperative placebo (n=231)
Events, n (%)	60 (24.8)	81 (35.1)
Censored patients, n (%)	182 (75.2)	150 (64.9)
Median DFS, months (95% CI)[a] DFS at 12 months, % (95% CI) DFS at 24 months, % (95% CI) DFS at 36 months, % (95% CI)	NR (NR-NR) 81.0 (75.2-85.5) 75.1 (68.7-80.4) 71.2 (63.8-77.3)	NR (41.5-NR) 74.1 (67.8-79.3) 62.4 (55.2-68.8) 61.4 (54.0-68.0)
HR (95% CI)	0.66 (0.47-0.92)	
2-sided p-value	0.013652	

DCO 10 May 2024
Abbreviations: DCO, data cut-off; DFS, disease-free survival; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumours
[a] Calculated using the Kaplan-Meier technique.
Source: AstraZeneca 2024[1]

Figure 2. Kaplan-Meier plot of disease-free survival assessed by BICR per RECIST 1.1 at AEGEAN IA2, resected mITT population



DCO 10 May 2024
Note: Durvalumab and placebo refer to the perioperative durvalumab and the perioperative placebo arms in AEGEAN. Circles indicate censored observations.
Abbreviations: CI, confidence interval; DCO, data cut-off; DFS, disease-free survival; mITT, modified intention to treat; NR, not reached
Source: AstraZeneca 2024[1]

1.1.6 Overall Survival

At IA2, an updated descriptive analysis of overall survival (OS) with 35% data maturity provided a HR of 0.89 (95% CI 0.70 to 1.14). This updated analysis included a total of 261 OS events in the mITT population (Table 3). Median OS was not reached for the perioperative durvalumab arm, compared to a median OS of 53.2 months in the perioperative placebo arm (Table 3 and Figure 3). The majority of death events in both arms were due to the disease under investigation: 76 patients (20.8%) in the perioperative durvalumab arm and 113 patients (30.2%) in the perioperative placebo arm.

Table 7. Overall survival at AEGEAN IA1 and IA2, mITT population

	IA1 (10 Nov 2022)		IA2 (10 May 2024)	
	Perioperative durvalumab (n=366)	**Perioperative placebo (n=374)**	**Perioperative durvalumab (n=366)**	**Perioperative placebo (n=374)**
Death, n (%)	81 (22.1)	82 (21.9)	121 (33.1)	140 (37.4)
Censored patients, n (%)	285 (77.9)	292 (78.1)	245 (66.9)	234 (62.6)
Median OS, months (95% CI)[a]	NR (NR-NR)	NR (NR-NR)	NR (NR-NR)	53.2 (44.3-NR)
OS at 12 months, % (95% CI)	83.6 (79.2-87.2)	85.9 (81.7-89.1)	84.3 (80.1-87.7)	85.3 (81.2-88.5)
OS at 24 months, % (95% CI)	71.7 (65.2-77.2)	72.0 (65.5-77.5)	74.4 (69.5-78.6)	72.2 (67.3-76.5)
OS at 36 months, % (95% CI)	NR	NR	67.1 (61.6-71.9)	63.9 (58.4-69.0)
HR (95% CI)	1.02 (0.75-1.39)		0.89 (0.70-1.14)	

Abbreviations: EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumours
[a] Calculated using the Kaplan-Meier technique.
Source: AstraZeneca 2024[1]

A pre-defined sensitivity analysis of OS, which censored patients whose primary cause of death was COVID-19 on their date of death, showed a numerically improved OS HR in favour of the perioperative durvalumab arm at IA2 (HR 0.84 [95% CI 0.66 to 1.08]).

1.1.7 Adverse Event Overview

Exposure

At IA2, all patients had completed the study treatment and the 90-day safety follow-up period. At IA2, the median actual duration of exposure to durvalumab/placebo was 40 weeks for the perioperative durvalumab arm and 36 weeks for the perioperative placebo arm. Among patients in the safety analysis set (SAS) population who received adjuvant treatment (266 patients in the perioperative durvalumab arm and 254 patients in the perioperative placebo arm), 68.4% of patients in the perioperative durvalumab arm and 63.4% in the perioperative placebo arm completed all 12 planned adjuvant treatment cycles

Adverse Events

At IA2, the proportions of patients in each arm with adverse events (AEs) in the categories reported in Table 4 remained similar to those observed at IA1. Most of the AEs reported were non-serious and low in severity (CTCAE Grade 1-2) in both treatment arms. The safety profile of durvalumab remained consistent with that reported at IA1. Of note, one additional patient in the perioperative durvalumab arm reported an AE of maximum Grade 3-4 (neutrophil count decreased) at IA2. No new AEs leading to discontinuation of durvalumab/placebo were reported in either treatment arm for the overall period at IA2 (Table 8).

The proportions of patients with serious adverse events (SAEs) in the perioperative durvalumab arm (39.2%) and the perioperative placebo arm (31.7%) remained similar to those reported at IA1. No additional AEs with an outcome of death were reported at IA2.

Table 8. Summary of any grade AEs at AEGEAN IA2 in the overall study period, safety analysis set

Overall study period[a]	Perioperative durvalumab (n=401)	Perioperative placebo (n=398)
AEs of any grade and any cause, n (%)	**387 (96.5)**	**379 (95.2)**
Maximum grade 3 or 4	175 (43.6)	172 (43.2)
Serious adverse events	157 (39.2)	126 (31.4)
Events leading to death	23 (5.7)	15 (3.8)
Leading to discontinuation of any study treatment	78 (19.5)	39 (9.8)
Discontinuation of durvalumab or placebo	51 (12.7)	25 (6.3)
Discontinuation of any chemotherapy	48 (12.0)	30 (7.5)
Discontinuation of both durvalumab or placebo and any chemotherapy	20 (5.0)	15 (3.8)
Leading to cancellation of surgery	7 (1.7)	4 (1.0)
AEs of any grade possibly related to durvalumab, placebo or chemotherapy, n (%)	**350 (87.3)**	**325 (81.7)**
Maximum grade 3 or 4	134 (33.4)	133 (33.4)
Events leading to death[b]	7 (1.7)	2 (0.5)
Any immune-related AE	**104 (25.4)**	**41 (10.3)**
Any grade 3 or 4	18 (4.5)	10 (2.5)

DCO 10 May 2024
Abbreviations: AE, adverse events; DCO, data cut-off
[a] First dose of study treatment until the earliest of: the last dose of study treatment or surgery (taking the latest dose or date of surgery +90 days, date of the first dose of subsequent anti-cancer therapy, or DCO date.
Source: AstraZeneca 2024[1]

Immune-mediated Adverse Events

Similar to the previous IA1 results, at IA2, more patients experienced any immune-mediated adverse event (IMAE) in the perioperative durvalumab arm (25.4%) than in the perioperative placebo arm (10.3%) in the overall period of the study (Table 5). The majority of IMAEs reported were non-serious, low in severity (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1-2), generally manageable, and resolved by the IA2 date in both treatment arms. There were no new IMAEs with outcome of death at IA2. Overall, there were five IMAEs with outcome of death in the perioperative durvalumab arm (1.2%) and none in the

perioperative placebo arm. The most common IMAEs occurring in ≥ 1% of patients overall are presented in Table 9.

IMAEs leading to discontinuation of any study treatment continued to be low in frequency in both treatment arms at IA2: 19 patients (4.7%) in the perioperative durvalumab arm and 4 (1.0%) in the perioperative placebo arm.

At IA2, the nature, severity, and manageability of IMAEs in the perioperative durvalumab arm remained consistent with the established safety profile of durvalumab.

Table 9. Summary of IMAEs at AEGEAN IA2 in the overall study period, safety analysis set

Overall study period[a]	**Perioperative durvalumab (n=401)**	**Perioperative placebo (n=398)**
Any IMAE[b], n (%)	**102 (52.4)**	**41 (10.3)**
Grade 3 or 4	18 (4.5)	10 (2.5)
IMAE categories reported in ≥1% of patients		
Pneumonitis	18 (4.5)	7 (1.8)
Grade 3-4	6 (1.5)	4 (1.0)
Hypothyroid events	42 (10.5)	10 (2.5)
Grade 3-4	0	0
Rash/dermatitis	22 (5.5)	7 (1.8)
Grade 3-4	2 (0.5)	1 (0.3)
Colitis/diarrhoea	3 (0.7)	5 (1.3)
Grade 3-4	0	3 (0.8)
Hepatic events	13 (3.2)	4 (1.0)
Grade 3-4	8 (2.0)	1 (0.3)

DCO 10 May 2024
Abbreviations: AE, adverse events; DCO, data cut-off
[a] First dose of study treatment until the earliest of: the last dose of study treatment or surgery (taking the latest dose or date of surgery +90 days, date of the first dose of subsequent anti-cancer therapy, or DCO date.
[b] An AE of special interest consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology, and requiring the use of systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therap. One patient assigned to the placebo arm erroneously received a single cycle of durvalumab and was included in the durvalumab arm for the safety analyses.
Source: AstraZeneca 2024[1]

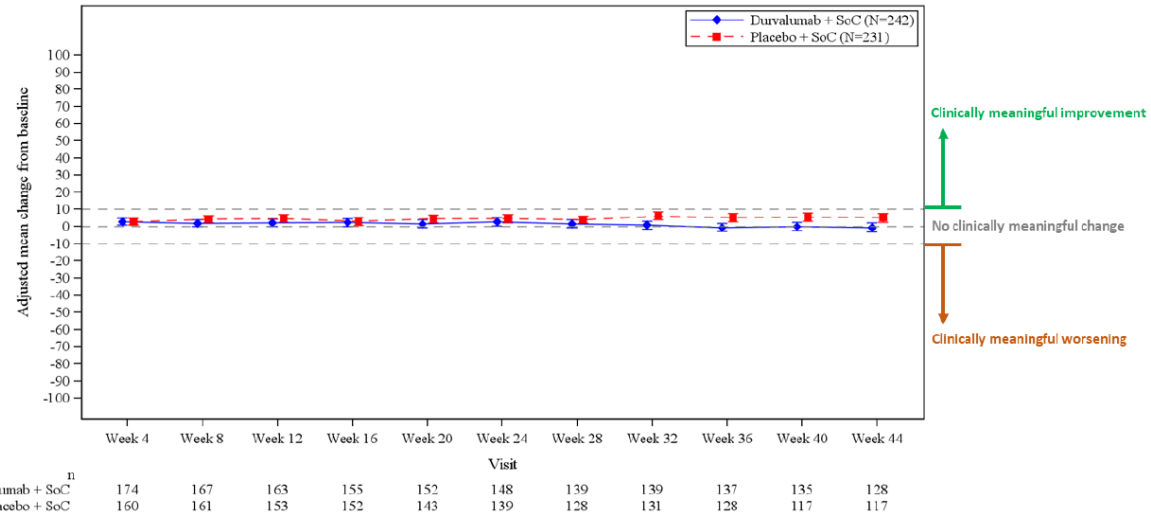
Deaths

The total number of deaths reported at IA2 in the ITT population continued to be lower in the perioperative durvalumab arm (128 patients [32%]) than the perioperative placebo arm (150 patients [37.3%]). In both study arms, most deaths continued to be attributed to the disease under investigation only (83/128 patients [64.8%] in the perioperative durvalumab arm and 121/150 [80.7%] in the perioperative placebo arm). Overall, the total number of patients in the SAS population who reported AEs with an outcome of death remained the same as reported at IA1 and IA2: 23 patients (5.7%) in the perioperative durvalumab arm and 15 patients (3.8%) in the perioperative placebo arm.

1.1.8 Health-Related Quality of Life

Overall, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) data collected after surgery indicate that adjuvant durvalumab treatment did not have a detrimental effect on patients' perception of global health status/quality of life, functioning, and disease/treatment-related symptoms. All questionnaire domain scores remained stable or improved slightly in both treatment arms throughout the adjuvant period of AEGEAN and were comparable to those observed in the general population (Figure 3).

Figure 3. Adjusted mean change from adjuvant baseline in EORTC QLQ-C30 scores by MMRM analysis at AEGEAN IA2, resected mITT population



DCO 10 May 2024
Note: Durvalumab and placebo refer to the perioperative durvalumab and the perioperative placebo arms in AEGEAN. Circles indicate censored observations.
Abbreviations: CI, confidence interval; DCO, data cut-off; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; mITT, modified intention to treat; NR, not reached
Source: AstraZeneca 2024[1]

1.2 Updated Match-Adjusted Indirect Comparison Results

For the original submission, anchored MAIC analyses were performed to compare the efficacy of perioperative durvalumab from AEGEAN[3] with neoadjuvant nivolumab + platinum-doublet chemotherapy (PDC) from CheckMate 816[4] leveraging the common comparator arm of neoadjuvant PDC (with or without perioperative placebo) in both studies. This is recommended by the NICE Decision Support Unit Technical Support Document (DSU TSD) 18 as a population-adjusted indirect comparison (PAIC) approach when there is evidence of imbalances in possible effect modifiers across trials.[5]

Due to the availability of new data for both trials, the MAIC has been updated using AEGEAN EFS data from IA2 (DCO 10 May 2024) (stratified HR 0.69 at IA2[1] versus 0.68 at IA1 (DCO 10 November 2022)[3]) and the 4-year results for CheckMate 816 (HR 0.66 at 4-year update[6] vs 0.68 at 3-year update[4]).

1.2.1 Methods

As in the original submission, MAIC analyses were conducted for the overall study period, alongside additional analyses using a piecewise approach, dividing into intervals of 0-to-3-months and 3+ months. A piecewise Cox model with a cut-point at 3 months from randomisation, was considered in addition to the standard indirect treatment comparison (ITC) to account for non-proportionality in EFS KM curves and to coincide with the timing of the first pre-surgery tumour assessment in AEGEAN. EFS KM curves from CheckMate 816 were digitized and pseudo patient-level data (PLD) recovered to estimate the corresponding piecewise HRs from CheckMate 816. Bucher ITCs were applied comparing the weighted HR estimated from the AEGEAN data at each cut-point vs that estimated from CheckMate 816 . BICR assessed EFS as the primary endpoint in AEGEAN was compared against BICR assessed EFS as the primary endpoint in CheckMate 816.

Three different scenarios were considered for the weighting: base case, scenario 1 (scenario analysis), and scenario 2 (sensitivity analysis [base case + Eastern Cooperative Oncology Group (ECOG)]). There was no change to the list of baseline characteristics included in the weighting, with base case including all possible effect modifiers (planned platinum chemotherapy, histology, PD-L1 expression, region, sex, smoking status, and stage). Matching was performed on a study as opposed to treatment level. Approximately 7% of patients had unevaluable PD-L1 status at baseline in CheckMate 816 and for the purposes of matching, proportions were calculated using the evaluable population as the denominator.

After weighting, the baseline characteristics in AEGEAN matched those in CheckMate 816 for those variables that were included in the weighting. The effective sample size (ESS) in AEGEAN after weighting to CheckMate 816 in each scenario is shown in Table 10.

Table 10. ESS of AEGEAN (weighted to match CheckMate 816) in the base case and scenario analyses

Arm	Scenario	N	Mean weight	Median weight	Sd weight	Min weight	Max weight	ESS (%)
Perioperative durvalumab	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative placebo	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative durvalumab	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative placebo	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative durvalumab	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative placebo	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18[5] planned platinum chemotherapy, PD-L1 expression, region, stage, histology, sex and smoking status
Scenario 1 = weighting based on possible effect modifiers that are imbalanced between trials: planned platinum chemotherapy, PD-L1 expression, region, and stage
Scenario 2 = weighting based on base case plus ECOG.
Abbreviations: ESS, effective sample size; PDC, platinum-doublet chemotherapy

Cox regression analysis results of EFS for perioperative durvalumab versus perioperative placebo in the weighted AEGEAN population (after weighting to match CheckMate 816) are provided in Table 11. In all three scenarios, weighting to match the CheckMate 816 population improved the relative treatment benefit of perioperative durvalumab versus perioperative placebo compared to the unweighted HR.

Table 11. Cox regression analysis of EFS for perioperative durvalumab versus perioperative placebo in AEGEAN (unweighted and after weighting in the base case and scenario analyses)

Comparison	Scenario	EFS HR	LCL (95%)	UCL (95%)
Perioperative durvalumab versus perioperative placebo	Unweighted	[redacted]	[redacted]	[redacted]
	Base case	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]
	Scenario 2	[redacted]	[redacted]	[redacted]

Based on the unstratified Cox proportional hazard model.

Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18[5] planned platinum chemotherapy, PD-L1 expression, region, stage, histology, sex and smoking status

Scenario 1 = weighting based on possible effect modifiers that are imbalanced between trials: planned platinum chemotherapy, PD-L1 expression, region, and stage
Scenario 2 = weighting based on base case plus ECOG.

Abbreviations: EFS, event-free survival, HR, hazard ratio; LCL, lower control limit; PDC, platinum-doublet chemotherapy; UCL, upper control limit

For the piecewise analysis of AEGEAN and CheckMate 816, a Cox regression model with an interaction between the timepoint indicator variable and treatment was used to obtain an estimate of the timepoint-specific (piecewise) HRs within the CheckMate 816 population. Event numbers before weighting for 0-to-3-months and 3+ months time intervals are presented in Table 12.

Table 12. Distribution of EFS events by piecewise cut-point

Treatment	Timepoint	N	Events	Maturity
Durvalumab 1500mg q3w + SoC	<3 months	[redacted]	[redacted]	[redacted]
Durvalumab 1500mg q3w + SoC	≥3 months	[redacted]	[redacted]	[redacted]
Nivolumab	<3 months	[redacted]	[redacted]	[redacted]
Nivolumab	≥3 months	[redacted]	[redacted]	[redacted]
Placebo (CheckMate 816)	<3 months	[redacted]	[redacted]	[redacted]
Placebo (CheckMate 816)	≥3 months	[redacted]	[redacted]	[redacted]
Placebo 1500mg q3w + SoC (AEGEAN)	<3 months	[redacted]	[redacted]	[redacted]
Placebo 1500mg q3w + SoC (AEGEAN)	≥3 months	[redacted]	[redacted]	[redacted]

Abbreviations: mg, milligram; q3w, every 3 weeks; SoC, standard of care

1.2.2 Results

The results for the overall trial period are consistent with the MAIC performed in the original submission for base case and scenario 1. The addition of ECOG as a possible effect modifier to base case in scenario 2 resulted in a slightly improved EFS HR in favour of perioperative durvalumab.

For the overall trial period base case analysis, after weighting AEGEAN to match the CheckMate 816 population more closely, an improvement in EFS was estimated for perioperative durvalumab versus neoadjuvant nivolumab + PDC (HR [redacted]), with an EFS HR of [redacted] (95% CI [redacted] to [redacted]) (Table 13).

An improvement in EFS was also estimated in scenario 1. This contrasts with the results of the unweighted ITC (HR[redacted]), demonstrating the impact of weighting and the need to account for imbalances in possible effect modifiers between trials.

Table 13. MAIC EFS HRs for the overall trial period comparing perioperative durvalumab versus neoadjuvant nivolumab + PDC (unweighted and after weighting in the base case and scenario analyses)

Comparison	Scenario	EFS HR	LCL (95%)	UCL (95%)
Perioperative durvalumab versus neoadjuvant nivolumab + PDC	Unweighted	[redacted]	[redacted]	[redacted]
	Base case	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]
	Scenario 2	[redacted]	[redacted]	[redacted]

Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18[5] planned platinum chemotherapy, PD-L1 expression, region, stage, histology, sex and smoking status

Scenario 1 = weighting based on possible effect modifiers that are imbalanced between trials: planned platinum chemotherapy, PD-L1 expression, region, and stage
Scenario 2 = weighting based on base case plus ECOG.

Abbreviations: EFS, event-free survival; HR, hazard ratio; LCL, lower control limit; PDC, platinum-doublet chemotherapy; UCL upper control limit

Similar trends (versus EFS IA1 analyses) are also seen with piecewise analyses. The results of the piecewise analyses are shown in Table 14. For the piecewise MAIC in the 3+ month time interval, which is when the majority of events occurred in each trial, the results of the MAICs were similar to those in the overall trial period. After weighting, improvements in EFS (3+ months) were estimated for perioperative durvalumab versus neoadjuvant nivolumab + PDC (HR [redacted]), with an EFS HR of [redacted] (95% CI [redacted] to [redacted]), in the base case analysis, [redacted] (95% CI [redacted] to [redacted]) in scenario 1, and [redacted] (95% CI [redacted] to [redacted]) in scenario 2.

Table 14. MAIC piecewise EFS HRs (0-to-3-months and 3+ month time intervals) for perioperative durvalumab versus neoadjuvant nivolumab + PDC (unweighted and after weighting in the base case and scenario analyses)

		0–3m time interval			3+m time interval		
Comparison	**Scenario**	**EFS HR**	**LCL (95%)**	**UCL (95%)**	**EFS HR**	**LCL (95%)**	**UCL (95%)**
Perioperative durvalumab versus neoadjuvant nivolumab + PDC	Unweighted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18[5]: planned platinum chemotherapy, PD-L1 expression, region, stage, histology, sex and smoking status

Scenario 1 = weighting based on possible effect modifiers that are imbalanced between trials: planned platinum chemotherapy, PD-L1 expression, region, and stage
Scenario 2 = weighting based on base case plus ECOG

Abbreviations: EFS, event-free survival; HR, hazard ratio; LCL, lower control limit; m, month; PDC, platinum-doublet chemotherapy; UCL upper control limit

In conclusion, results of the MAIC were largely unchanged between EFS IA1 and IA2 analyses. There were numerical improvements with perioperative durvalumab versus neoadjuvant nivolumab (but not nominally statistically significant, with wide 95% CIs), indicating a potential benefit of perioperative durvalumab and continuation of immuno-oncology therapy following surgical resection.

1.3 Updated Network-Meta Analysis Results

The NMA was also updated to include EFS data from the IA2 of AEGEAN (DCO 10 May 2024)(mITT population).

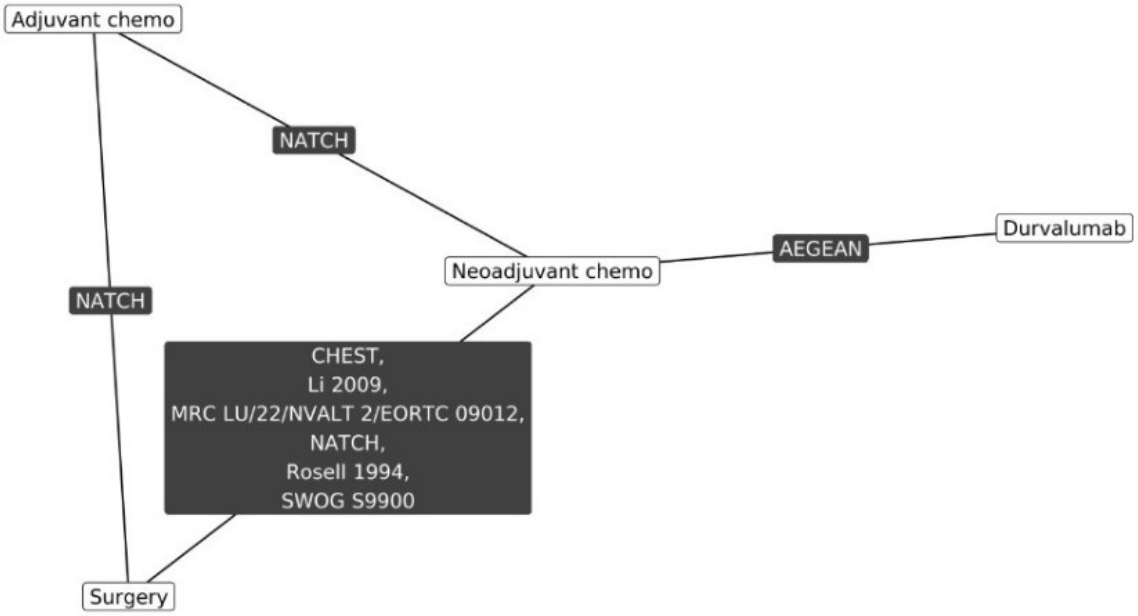
1.3.1 Methods

As in the MAIC, piecewise NMAs with 0 to 3 month and 3+ month time intervals were conducted in addition to the conventional NMA for the overall trial period to account for the delayed separation of EFS curves in the AEGEAN trial.

The updated NMA was conducted in a Bayesian framework using R version 4.0.2, as in the original NMA.[7] Log HRs were analysed using normal likelihood and identity link. Uninformative priors were used for treatment effects. Fixed and random effects models were run, but there was limited data to estimate between-study heterogeneity, so informative priors based on a log-normal distribution ('subjective outcomes (various)' prior, log-normal ~ (-2.93, 1.582)) were used based on Turner et al.[8] Models were fitted using 'stan': 10,000 iterations (burn-in 5,000), keeping every second iteration (ie, thinning = 2) from four chains.

The fixed effects model assumed a single 'true' effect size underlying the trials informing a treatment comparison (ie, differences between studies are purely due to chance variation). The random effects model assumed studies informing a treatment comparison estimated 'similar' effects, but there were difference beyond chance variation (ie, total variation = chance differences + between-study heterogeneity). The network of evidence for the base case analysis versus adjuvant PDC and surgery alone is shown in Figure 4.

Figure 4. Network diagram of mITT AEGEAN versus adjuvant chemotherapy and surgery alone, base case



Abbreviations: chemo, chemotherapy; mITT, modified intent-to treat

1.3.2 Results

The model fit statistics of the fixed- and random effects models for the EFS NMA (overall period and 3+ months piecewise analyses) are presented in Table 15 and Table 16. The HRs, including 95% credible intervals (CrIs) for comparisons of perioperative durvalumab versus each comparator, for both random- and fixed-effect models, computed for the overall period and 3+ months data, are presented in Figure 5 (base case) and Figure 5 to Figure 9 (sensitivity analyses).

Overall, the results of the updated NMA are consistent with those in the original submission. In all cases, the EFS HRs were in favour of perioperative durvalumab versus each of the comparators. In the preferred random effects models, there were numeric benefits associated with perioperative durvalumab. In the fixed effect models, the differences between perioperative durvalumab and each comparator were nominally statistically significant (upper 95% CrI <1). Consistent with the original submission, sensitivity analyses 2 results in the greatest precision (narrower 95% CrIs). The results of sensitivity analysis 2 were used as estimates of relative efficacy in the cost-effectiveness model.

Table 15. Model fit statistics for EFS NMA, overall period, mITT

Analysis	Treatment effects	Data points	Residual deviance	Effective parameters, pD	DIC
Base case	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 1	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]

Sensitivity analysis 2	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 3	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 4	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]

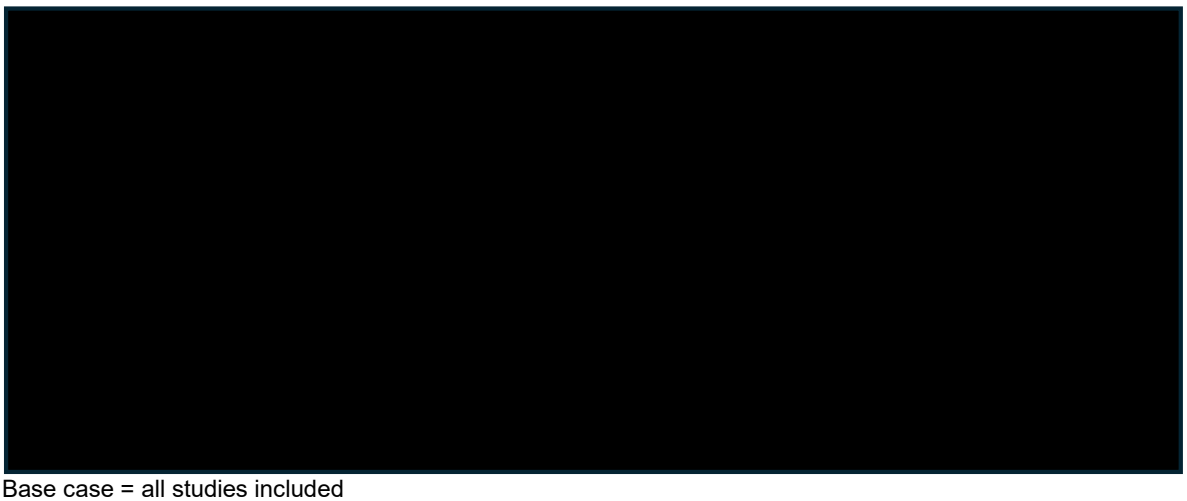
Abbreviations: DIC, deviance information criteria; EFS, event-free survival; mITT, modified intent-to treat; pD, posterior mean of the deviance

Table 16. Model fit statistics for EFS NMA, 3+ months, mITT

Analysis	Treatment. effects	Data points	Residual deviance	Effective parameters, pD	DIC
Base case	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 1	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 3	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 4	Fixed	[redacted]	[redacted]	[redacted]	[redacted]
	Random	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC, deviance information criteria; EFS, event-free survival; mITT, modified intent-to treat; pD, posterior mean of the deviance

Figure 5. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (base case)



Base case = all studies included

Abbreviations: chemo, chemotherapy; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat

Figure 6. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 1)

Sensitivity analysis 1 = Excludes Rosell 1994,[9-11] MRC LU/22/NVALT 2/EORTC 09012[12] (studies with 2G PDC)

Abbreviations: chemo, chemotherapy; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat

Figure 7. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 2)

Sensitivity analysis 2 = Excludes Rosell 1994,[9-11] Li 2009[13] (studies with stage III patients only)

Abbreviations: chemo, chemotherapy; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat

Figure 8. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 3)

Sensitivity analysis 3 = Excludes Li 2009[13] (Asia only studies)

Abbreviations: chemo, chemotherapy; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat

Figure 9. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 4)

Sensitivity analysis 4 = Excludes Rosell 1994,[9-11] MRC LU/22/NVALT 2/EORTC 09012,[12] Li 2009[13] (studies with 2G PDC, studies with stage III only patients, and Asia-only studies)

Abbreviations: chemo, chemotherapy; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat

1.4 Multilevel Network Meta-Regression Feasibility Assessment

After receiving the draft guidance, the company conducted a feasibility assessment for a multilevel network meta-regression (ML-NMR) analysis. As per the EAG clarification question A22, a ML-NMR was considered in which all relevant comparators (i.e. neoadjuvant nivolumab, adjuvant chemotherapy, surgery only and neoadjuvant chemotherapy) were included in the network.

The network for the ML-NMR therefore included those trials in the preferred network for the NMA (AEGEAN, NATCH, CHEST, MRC LU22/NVALT 2/EORTC 08012, and SWOG S9900), as well as CheckMate-816. Limited reporting of baseline characteristics which were

considered possible effect modifiers (i.e. smoking status and PD-L1 expression) across trials (for adjuvant chemotherapy and surgery) was noted.

There were also differences in staging systems and reported stage (by TNM or stage II/III) in these trials making it challenging to assess and adjust for differences between trials in disease stage. For example, staging system was only reported for the CHEST trial (5th edition, compared to the 7th edition used in CheckMate-816 and 8th edition used in AEGEAN), and not reported in the three other adjuvant chemotherapy/surgery trials in the network. The covariates which would have been included in the ML-NMR would therefore have been restricted to baseline characteristics available across all studies (sex, region, planned platinum chemotherapy and histology). This limitation was originally concluded in the company response to EAG clarification question A22, in which the EAG requested a m ML-NMR. Only including these baseline characteristics, and not other potential effect modifiers (such as disease stage, PD-L1 expression and smoking status), would therefore be a substantial limitation of the ML-NMR, which would result in highly uncertain results.

Age was not included as a covariate in the matching-adjusted indirect comparison and would not be included in the ML-NMR, as this is not a known or expected treatment-effect modifier. Adjusting for age is not expected to have a major impact on relative efficacy estimates in the indirect treatment comparisons (refer to Comment 2).

A key feature of ML-NMR is the ability to model treatment effect modification for all treatments in the network (i.e. population adjustment is carried out for all treatments). In doing so, ML-NMR can generate estimates of relative efficacy within any specified patient population. According to Phillippo 2020,[14] the data requirements for estimating a treatment effect and independent effect modifier interaction for a given treatment k are either:

- Individual patient data from one or more trials including treatment k or
- Sufficiently many aggregate data studies including treatment k, with enough variation in covariate values (of note, in Phillippo 2023,[15] five studies of aggregate data for a given treatment was considered to be insufficient)

Importantly, neither of the above criteria were satisfied for any of the other interventions: neoadjuvant nivolumab (one aggregate study), adjuvant chemotherapy (one aggregate study) or surgery (four aggregate studies). Therefore, the shared effect modifier assumption would need to be applied to all treatments included in a ML-NMR (perioperative durvalumab, neoadjuvant nivolumab, surgery, adjuvant chemotherapy). This borrows information of effect modification from the individual patient data trial (i.e. from AEGEAN) and assumes this effect is shared across all other treatments within the treatment set.

The shared effect modifier assumption in this network is fundamental for conducting a robust ML-NMR. Following an assessment of the available data for the studies in the network, the analysis was deemed implausible for the following reasons:

- There is heterogeneity of effect modifiers. For example, there are differences in treatment class (surgery only; chemotherapy plus surgery; immunotherapy plus chemotherapy and surgery) and treatment approaches (neoadjuvant only; adjuvant

only; perioperative) within the network. This heterogeneity can lead to biased estimates if the assumption is not met.

- Despite belonging to the same treatment class, it is not appropriate to assume the same effect modification between (perioperative) durvalumab and (neoadjuvant only) nivolumab, which are distinct treatment regimens. Contrary to the shared effect modifier assumption, the EFS subgroup analyses from AEGEAN and CheckMate-816 indicate that effect modification is not the same for perioperative durvalumab and neoadjuvant nivolumab. For example, in AEGEAN, EFS HRs versus neoadjuvant chemotherapy were largely consistent across PD-L1 subgroups (<1% and ≥1%) and histology subgroups (non-squamous and squamous), but larger differences between these subgroups were evident in the CheckMate-816 trial. Furthermore, in certain subgroups the direction of effect modification was different in each trial, e.g. in AEGEAN, a lower EFS HRs was reported in the planned cisplatin subgroup (planned platinum chemotherapy) and in males (gender). Whereas in CheckMate-816, a lower EFS HR was reported in the carboplatin subgroup and in females.

- Due to the sparse information available, with individual patient data available from the AEGEAN trial only, and with information for neoadjuvant nivolumab and adjuvant chemotherapy available from a single aggregate trial each (CheckMate-816 and NATCH, respectively), it is also not possible to test (i.e. with adequate power) the validity of the shared effect modifier assumption in this network using the methods described in Phillippo et al. 2023. ML-NMR provides a powerful tool for population-adjustment treatment comparisons. However, in this instance it is reliant on the strong assumption of shared effect modification, which is invalid for this network due to the clinical implausibility of the assumption (varying treatment classes and regimens).

Given the above limitations, it was not feasible to conduct a robust ML-NMR and this method was considered inappropriate to inform the comparative efficacy of durvalumab and relevant comparators.

1.5 Time-varying hazards analysis

Data from the AEGEAN study was used in two analyses to compare perioperative durvalumab against all comparators in the original submission:

1. Network meta-analysis (NMA) comparing against adjuvant chemotherapy and surgery alone

2. Matching adjusted indirect comparison (MAIC) comparing against neoadjuvant nivolumab from the CheckMate-816 study

Both of these analyses used a Cox proportional hazards model. A piece-wise approach was used whereby the analysis was split into 0-3 month and 3+ month time periods to avoid the issue of non-proportional hazards in the early stages of follow-up.

Following review, the external assessment group (EAG) and NICE committee requested that a time-varying hazard ratio approach is taken to the analyses listed above.

1.5.1 Methods

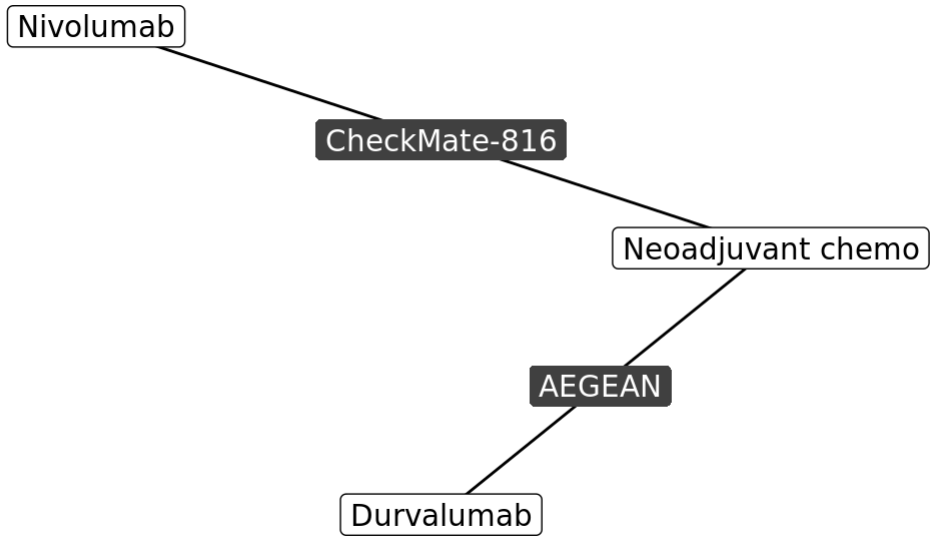
The time-varying hazards analysis follows the approach of Cope et al (2020)[16]; for each arm of each study in the analysis (reconstructed) survival data are fit to alternative survival distributions (Weibull, Gompertz, log-normal and log-logistic). For each distribution the scale and shape parameters are included in a multivariate NMA to obtain time-varying estimates of relative treatment effects. For the MAIC, the parametric models were fitted to weighted data from AEGEAN.

The multivariate NMA was conducted using JAGS with a fixed effects model; random effects models were fitted but due to the limited evidence base and lack of a plausible (weakly informative) prior for the between-study heterogeneity terms, the 95% CrIs were too wide to be of use.

1.5.2 Results for MAIC versus neoadjuvant nivolumab

The network diagram for the MAIC versus neoadjuvant nivolumab is shown in Figure 10.

Figure 10. Network diagram for the time-varying hazards analysis of perioperative durvalumab versus neoadjuvant nivolumab



The assessment of model fit based on AIC shows that a log-normal distribution best fits the nivolumab data from CheckMate 816 and Gompertz provides the best fit for the neoadjuvant PDC arm from CheckMate 816 and for both trial arms in AEGEAN (Table 17). Similarly, the Gompertz distribution provides the best visual fit to the KM-curves for both AEGEAN and CheckMate 816 (Figure 11). The Gompertz and the log-normal models both assume the hazard decreases monotonically (Figure 12), but log-normal, which was the second best-fitting distribution, allows for more flexibility in terms of arc-shaped hazards. Log-normal was therefore selected as the most appropriate curve.

The analysis shows that based on the fixed effect model and log-normal distribution, the EFS HR for perioperative durvalumab versus neoadjuvant nivolumab [redacted]

[redacted]. In comparison, the constant HR from the piecewise MAIC for the 3+ month time period is [redacted]. However, as indicated by the grey area in Figure 13 indicating the 95% credible interval, there is uncertainty around the result.

Table 17. Parametric survival model fit (AIC) for AEGEAN and CheckMate 816

Treatment	Weibull	Gompertz	Log-normal	Log-logistic
EFS - mITT - CheckMate-816				
Nivolumab	710.0	704.8	700.4	705.9
Neoadjuvant chemo	821.1	806.8	807.1	811.5
EFS - mITT - AEGEAN				
Durvalumab	1,044.8	1,019.4	1,025.8	1,038.1
Neoadjuvant chemo	1,523.2	1,484.9	1,488.0	1,502.6

Abbreviations: AIC; akaike information criterion; EFS, event-free survival; mITT, modified intention to treat

Figure 11. Parametric model fit – EFS – AEGEAN and CheckMate 816

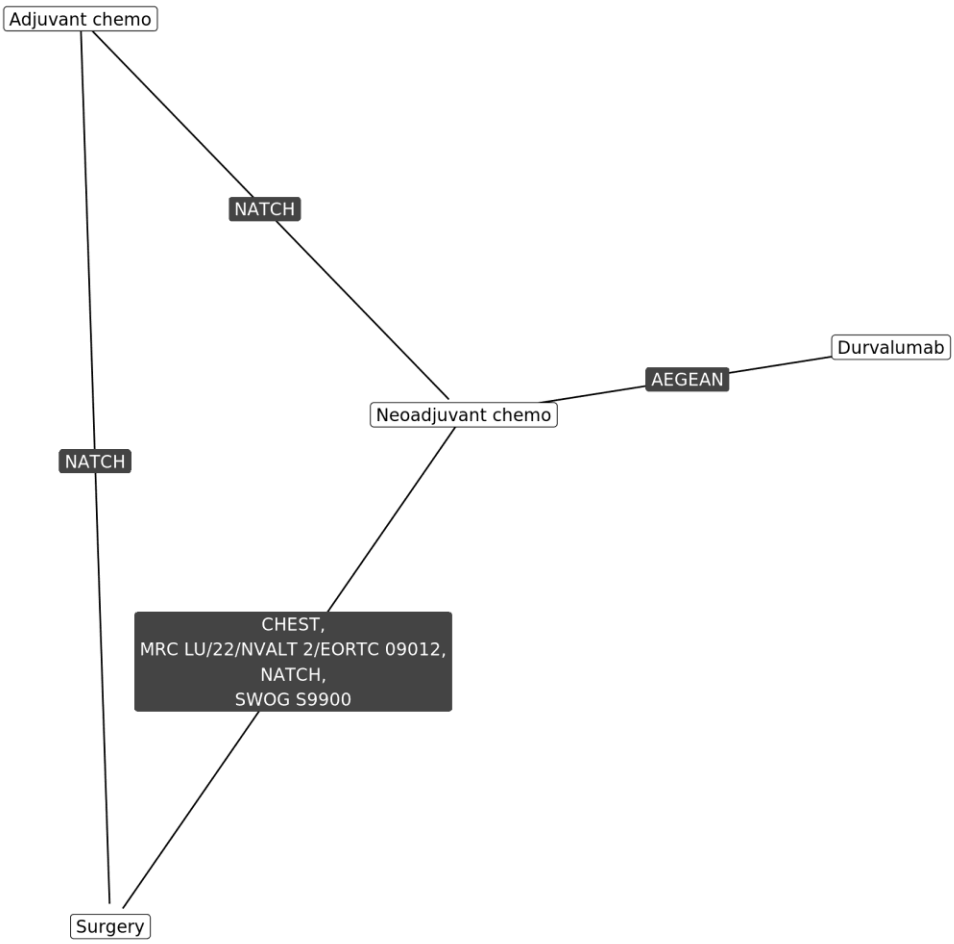
Figure 12. EFS hazard ratios for perioperative durvalumab vs neoadjuvant nivolumab over time – fixed effect model

Figure 13. EFS HR over time for perioperative durvalumab vs neoadjuvant nivolumab, fixed effect model (log-normal)

1.5.3 Results for NMA versus adjuvant PDC, neoadjuvant PDC and surgery alone

The network diagram for the NMA versus adjuvant PDC, neoadjuvant PDC and surgery alone is shown in Figure 14.

Figure 14. Network diagram for the time-varying hazards analysis of perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC and surgery alone



The assessment of model fit based on AIC shows that a log-normal distribution provides the best statistical fit for the majority of treatment arms in the trials in the NMA (Table 18). The visual fit of the different survival distributions to the KM-curves for each treatment arm in each trial is shown in Figure 15. Based on an assessment of the statistical and visual fit across all the treatments in the different trials, the log-normal distribution was considered to provide the best fit.

The analysis shows that based on the fixed effect model and log-normal distribution, the EFS HR for perioperative durvalumab versus adjuvant PDC [redacted] the constant HR from the piecewise NMA for the 3+ month time period at [redacted] (Figure 17). [redacted], the EFS HR for perioperative durvalumab versus neoadjuvant PDC was [redacted] the constant HR from the piecewise NMA for the 3+ month time period. The time-varying hazards analysis of perioperative durvalumab versus surgery showed an EFS HR [redacted] the constant HR for the 3+ month piecewise NMA.

Table 18. Parametric survival model fit (AIC) for the trials in the NMA

Treatment	Weibull	Gompertz	Log-normal	Log-logistic
EFS - mITT - CHEST				
Neoadjuvant chemo	671.7	662.7	662.2	666.1
Surgery	784.8	781.9	779.6	781.3
EFS - mITT - MRC LU/22/NVALT 2/EORTC 09012				
Neoadjuvant chemo	1,400.5	1,394.2	1,394.2	1,394.6
Surgery	1,453.9	1,442.1	1,437.4	1,444.2
EFS - mITT - NATCH				
Adjuvant chemo	1,163.1	1,159.6	1,154.2	1,156.0
Neoadjuvant chemo	1,185.4	1,176.0	1,172.1	1,176.7
Surgery	1,233.9	1,226.0	1,226.6	1,226.5
EFS - mITT - SWOG S9900				
Neoadjuvant chemo	1,120.5	1,094.4	1,099.5	1,106.5
Surgery	1,581.2	1,582.6	1,596.6	1,606.9
EFS - mITT - AEGEAN				
Durvalumab	1,259.5	1,234.2	1,236.5	1,249.6
Neoadjuvant chemo	1,547.9	1,520.3	1,515.8	1,529.8

Abbreviations: AIC; akaike information criterion; EFS, event-free survival; mITT, modified intention to treat

Figure 15. Parametric model fit – EFS - for the trials in the NMA

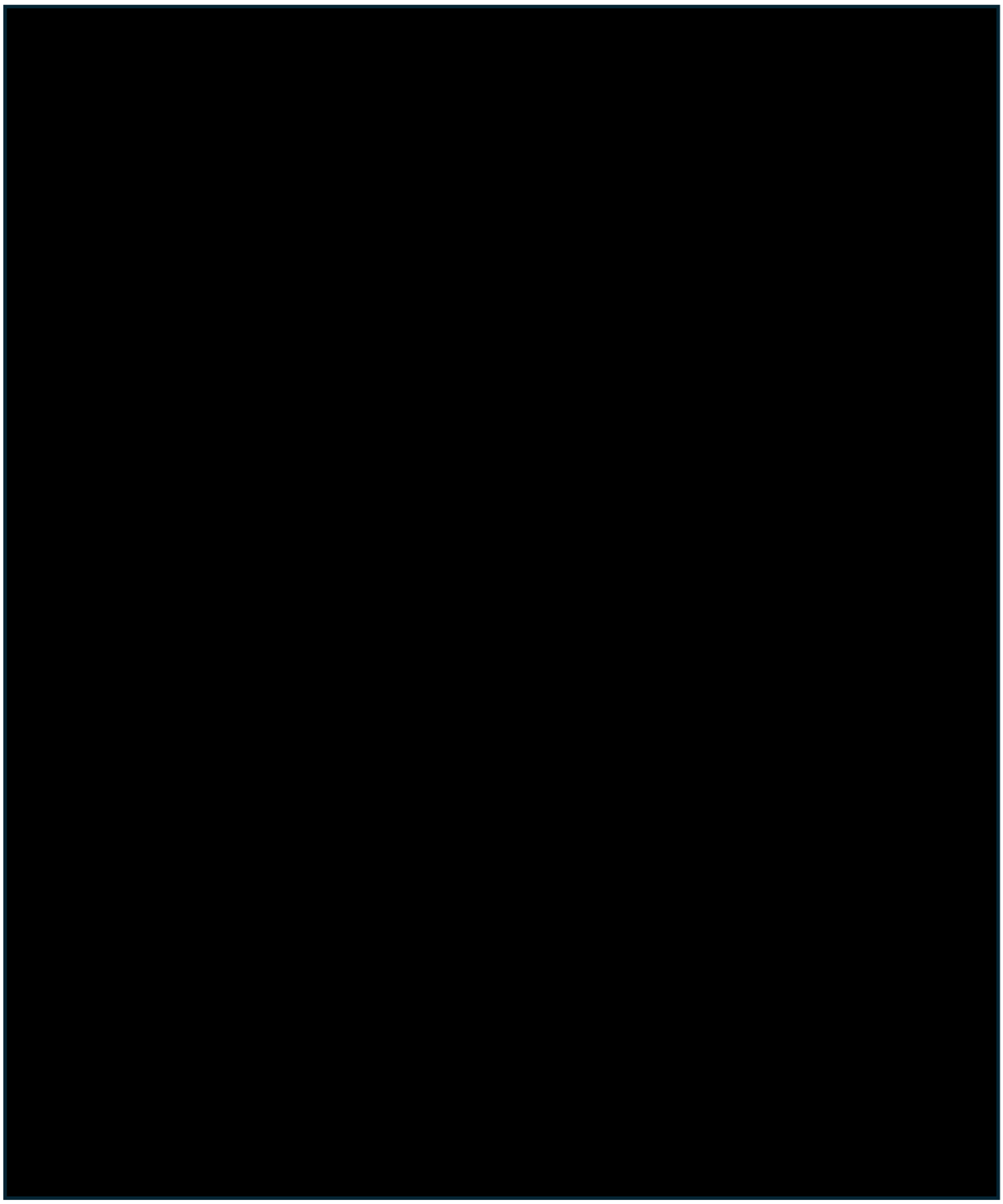


Figure 16. EFS hazard ratios for perioperative durvalumab vs comparators over time – fixed effect model

Figure 17. EFS HR over time for perioperative durvalumab vs comparators, fixed effect model (log-normal)

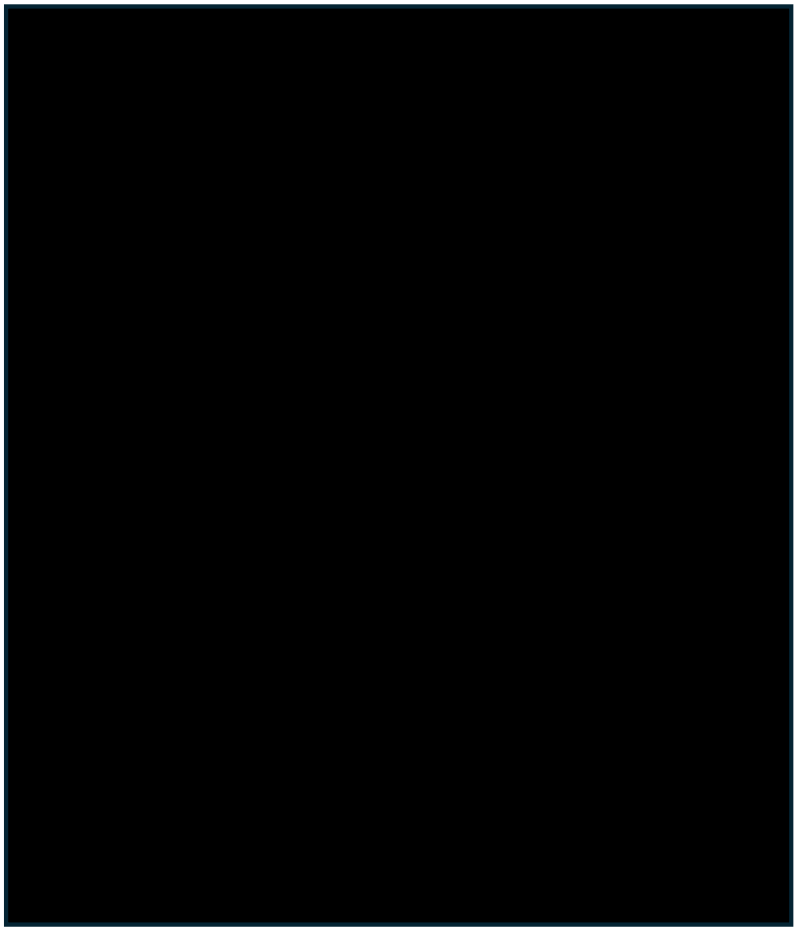
2 Additional Economic Evidence and Updated Cost-Effectiveness Results

2.1 Clinical parameters and variables

2.1.1 Modelling event-free health state

At IA2 (DCO 10 May 2024), an updated descriptive analysis of EFS was conducted. The EFS data maturity was 39%. Overall, the EFS results at IA2 were consistent with the IA1 results. The shape of the IA2 hazard plots from 3+ months indicate proportionality over time when using the piecewise approach; this is consistent with the analyses undertaken for IA1. This is observed in Figure 18, which shows the updated cumulative hazard plot (the 3-month time period being the turning point in terms of hazard function).

Figure 18. Log-cumulative hazard and smoothed Schoenfeld residuals plot for piecewise 3+ month interval; EFS



Abbreviations: EFS, event-free survival; mITT, modified intent-to-treat; SoC, standard of care

2.1.1.1 Neoadjuvant PDC from AEGEAN mITT population

Similar to IA1, the AEGEAN perioperative placebo arm was used to inform the efficacy of neoadjuvant PDC for IA2 also.

Statistical goodness of fit (AIC/BIC)

Statistical tests based on AIC and BIC scores for EFS IA2 (Table 27) were used to identify the best-fitting parametric distribution from month 3 onwards based on internal validity. The log-normal and log-logistic distributions were the best statistically fitting distributions for the neoadjuvant PDC arm (in terms of AIC and BIC). The exponential and Gompertz distribution were the worst-fitting distributions, according to AIC and BIC.

Table 19. Goodness of fit statistics for AEGEAN neoadjuvant PDC; EFS (post-3 months)

Neoadjuvant PDC				
Model	**AIC**	**AIC Rank**	**BIC**	**BIC Rank**

Exponential	1353.0	5	1356.8	5
Weibull	1283.0	3	1290.7	2
Log-normal	**1278.7**	**1**	**1286.3**	**1**
Log-logistic	**1278.7**	**1**	**1286.3**	**1**
Gompertz	1290.6	4	1298.3	4
Generalised gamma	1280.1	2	1291.6	3

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Visual fit to KM plot

Visual inspection was used to find the best fitting parametric distribution to the underlying data from three months onwards. Model fits for neoadjuvant PDC are presented in Figure 19. All parametric distributions appear to provide reasonable fits, except for the exponential distribution. Therefore, based on both the statistical and visual fits, the exponential and Gompertz models were not considered appropriate for the base case analyses.

Figure 19. Model fits to neoadjuvant PDC; EFS

Abbreviations: BICR, Blinded Independent Central Review; EFS, event-free survival; mITT, modified intention-to-treat; SoC, standard of care

Validation of long-term extrapolations

At IA2, to ensure that the transitions comprising EFS (i.e., EF to LRR, EF to DM, and EF to Death) were in line with the observed EFS data from AEGEAN, validation of model predictions against the observed EFS KM were performed. Figure 20 illustrates that the EFS IA2 predictions from all models were in line with the observed IA2 EFS from AEGEAN.

Figure 20. Long-term predictions; modelled EFS versus observed EFS from AEGEAN – IA2

Abbreviations: KM, Kaplan-Meier; PDC, platinum-doublet chemotherapy

Clinical plausibility of long-term extrapolations

At IA1, clinical expert opinion was sought to ensure that the best-fitting model provides a clinically plausible extrapolation beyond the trial data. In a UK clinical advisory board, the majority of clinical experts agreed that the extrapolation provided by the log-normal was the most clinically plausible in this patient population based on [redacted] of patients event-free at 60 months.[17] All other survival extrapolations were considered to underestimate the proportion of patients event free at 5 years and therefore were not deemed clinically plausible. Therefore, the 5-year prediction using the log-normal extrapolation for IA2 EFS data at [redacted] is consistent with clinical expectations.

The EFS survival landmarks for neoadjuvant PDC with different EFS distributions are presented in Table 20.

Table 20. Event-free survival landmarks (Neoadjuvant PDC)

EFS	12 months	24 months	36 months	48 months	60 months
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EFS, event-free survival

Based on the above, and in line with IA1, the log-normal was determined to be the most appropriate model to use in the IA2 base case analyses. The log-normal model provides a reasonable visual fit to the observed EFS IA2 data, performs very well in terms of statistical fit and produces a 5-year EFS prediction that is aligned with clinician expectations based on the UK advisory board conducted in January 2024.[17]

The availability of more mature OS data at EFS IA2 and a longer follow-up also enabled the comparisons of the EFS distributions with respect to OS predictions. Overall, the log-normal EFS distribution predicted OS reasonably well, consistent with the AEGEAN EFS IA2 OS data. The survival landmarks when using the lognormal distribution for EFS are in line with the reported OS landmarks for AEGEAN (at 12, 24, 36 and 48 months) and/or their 95% CIs.

The OS survival landmarks and 95% CIs (for the KM data only) for neoadjuvant PDC when using different EFS distributions are shown in Table 21.

Table 21. Overall survival landmarks (Neoadjuvant PDC)

	OS % (95% CI)				
	12 months	24 months	36 months	48 months	60 months
Kaplan-Meier	[redacted]	[redacted]	[redacted]	[redacted]	-
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; OS, overall survival

2.1.1.2 Perioperative durvalumab from AEGEAN

Similar to IA1, the perioperative durvalumab EFS efficacy was modelled in IA2 by applying a HR to the neoadjuvant PDC arm. First, the efficacy was informed by the neoadjuvant PDC AEGEAN EFS IA2 KM data and from month three onwards, EFS was modelled by applying a HR to the extrapolated EFS for neoadjuvant PDC. The HRs for perioperative durvalumab versus neoadjuvant PDC used in the model were all based on the 3-month piecewise EFS IA2 ITC analyses.

As per the original submission, the cost-effectiveness model also enables a comparison using the unadjusted EFS HR for perioperative durvalumab versus placebo + PDC, which was used in the NMA to simulate the effectiveness in the unadjusted AEGEAN mITT population. The unadjusted HR can be used as an alternative for comparing perioperative durvalumab with all comparators, except for neoadjuvant nivolumab + PDC. This is because such a comparison would lack robustness and would not account for potential treatment effect modifiers; hence,

only the MAIC-adjusted HR is employed to assess the comparison between nivolumab + PDC and perioperative durvalumab. Since neoadjuvant nivolumab is considered the main comparator, the unadjusted HR is provided here for completeness only.

Table 22 provides an overview of the piecewise HRs used to inform the post-3 months EFS efficacy for perioperative durvalumab. The model predicted EFS for the perioperative durvalumab arm, the MAIC-adjusted KM data and the EFS landmarks are presented in Figure 21 and Table 23, respectively.

Table 22. Piecewise (post-3 months) HRs for perioperative durvalumab vs. neoadjuvant PDC across the different settings

EFS HR	Comparison	Piecewise HR	Lower 95% CI	Upper 95% CI	Source
Comparison vs. neoadjuvant PDC, neoadjuvant nivolumab, surgery alone and adjuvant PDC (*base case*)	Perioperative durvalumab vs. neoadjuvant PDC	[redacted]	[redacted]	[redacted]	Weighted AEGEAN piecewise HR (3+ months) after weighting to CheckMate-816 in the MAIC Base case; including all effect modifiers
Comparison vs. neoadjuvant PDC, surgery alone and adjuvant PDC (*alternative base case*)		[redacted]	[redacted]	[redacted]	AEGEAN piecewise HR (3+ months) in mITT, used in NMA (mITT)

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PDC, platinum-doublet chemotherapy

Figure 21. Five-year predictions: modelled EFS versus observed EFS from AEGEAN (weighted from the MAIC against CheckMate-816) – base case

Abbreviations: EFS, event-free survival

Table 23. Event-free survival landmarks (Perioperative durvalumab – base case)

EFS	12 months	24 months	36 months	48 months	60 months
Kaplan-Meier†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† based on AEGEAN weighted from the MAIC against CheckMate-816
Abbreviations: EFS, event-free survival

2.1.1.3 EFS comparator efficacy

The following therapies, which are not part of the AEGEAN trial, were included as comparators within the cost effectiveness model:

- Neoadjuvant nivolumab + PDC
- Surgery alone
- Adjuvant PDC

Following the updated EFS data for IA2, the MAIC and NMA informing comparator efficacy were also updated. Overall, results of the MAIC and NMA were largely unchanged between EFS IA1 and IA2 analyses. Across each of the comparisons, the EFS HRs were in favour of perioperative durvalumab.

2.1.1.3.1 Neoadjuvant nivolumab + PDC (CheckMate-816)

EFS IA2 (DCO 10 May 2024) (mITT population) data from AEGEAN and updated 4-year data of CheckMate-816 were included in the updated MAIC.[18] From month three onwards, the EFS efficacy was modelled via a piecewise HR applied to the EFS curve of neoadjuvant PDC (Table 24).

Table 24. Piecewise (post-3 months) EFS comparator efficacy (neoadjuvant nivolumab + PDC) – IA2

Treatment	Piecewise HR	Lower 95% CI	Upper 95% CI	AEGEAN Reference arm	Source
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	PBO (i.e., neoadjuvant PDC)	Estimated piecewise HR (3+ months) from pseudo-patient level data derived from the CheckMate-816 4-year EFS KM, as used in the MAIC

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; PBO, placebo; PDC, platinum-doublet chemotherapy

2.1.1.3.2 Surgery alone and adjuvant PDC

The NMA was also updated to include EFS data from the IA2 of AEGEAN (DCO 10 May 2024)(mITT population). From month three onwards, the EFS efficacy of both comparators was modelled via a piecewise HR applied to the EFS curve of neoadjuvant PDC (Table 25).

Table 25. Piecewise (post-3 months) EFS comparator efficacy (surgery alone and adjuvant PDC) – IA2

Treatment	Piecewise HR	Lower 95% CI	Upper 95% CI	AEGEAN Reference arm	Source
Surgery alone	[redacted]	[redacted]	[redacted]	PBO (i.e., neoadjuvant PDC)	Piecewise NMA (3+ months) in AEGEAN mITT; Sensitivity analysis 2; random effects
Adjuvant PDC	[redacted]	[redacted]	[redacted]	PBO (i.e., neoadjuvant PDC)	Piecewise NMA (3+ months) in AEGEAN mITT; Sensitivity analysis 2; random effects

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; PBO, placebo; PDC, platinum-doublet chemotherapy

2.1.1.4 TP1 and TP2: Event-free (EF) to LRR or DM

As discussed in the original submission, clinical experts in a UK advisory board were presented with probabilities obtained from exploratory, post-hoc analyses of the AEGEAN trial on the site of RECIST recurrence EFS events.[17] The analyses indicated that [redacted] experienced a local event, while [redacted] experienced a distant event. However, the clinical experts reached a consensus that, in clinical practice, a greater proportion of patients transition to the DM state. The clinical opinion concluded that a [redacted] probability of transitioning to LRR and a [redacted] probability of transitioning to DM if a non-death EFS event occurs would be more appropriate.

However, the NICE committee concluded that the base-case should include the AEGEAN trial analysis data on the site of recurrence (i.e., [redacted] for LRR vs. [redacted] for DM), rather than the figures validated by clinical experts. Hence, the updated base-case now includes the NICE preferred assumption.

The committee acknowledged that changing the proportions did not have a large impact on the cost-effectiveness estimates. Nevertheless, the original submission's base-case assumption (i.e., figures suggested by clinical experts [redacted] vs. [redacted]) was included as a scenario analysis (see Table 26).

The same proportions in terms of site of recurrence (to LRR or DM) were used for the non-AEGEAN comparators as those estimated for perioperative durvalumab and neoadjuvant PDC.

Table 26. Site of recurrence inputs for EF

Treatment arm	Site of recurrence events		Justification
	% LRR	% DM	
Base-case			
Perioperative durvalumab	[redacted]	[redacted]	AEGEAN EFS by site of recurrence data (pooled across treatment arms in line with TA823)[19]
Neoadjuvant PDC (and all non-AEGEAN comparators)	[redacted]	[redacted]	
Scenario 1:			
Perioperative durvalumab	[redacted]	[redacted]	

Neoadjuvant PDC (and all non-AEGEAN comparators)	[redacted]	[redacted]	UK clinician validation[17]

Abbreviations: DM, distant metastasis; LRR, locoregional recurrence; SoC, NSCLC, non-small cell lung cancer; standard of care

2.1.1.5 TP3: Event-free (EF) to Death

For the transition from EF to death, updated EFS data from AEGEAN IA2 (DCO 10 May 2024) were used. Similar to IA1, in IA2 the data from the perioperative durvalumab and neoadjuvant PDC arms were pooled, due to the relative immaturity of the AEGEAN trial data to populate the EF to death transition [redacted]

As in IA1, standard parametric distributions were applied in order to extrapolate the pooled time to death as first EFS event data. Statistical tests based on AIC and BIC scores (Table 27) were used to identify the best-fitting parametric distribution based on internal validity. The log-normal distribution was selected to extrapolate the data because it represented an appropriate statistical fit, provided a good visual fit to the observed KM data and ensured consistency with the EFS extrapolation.

Table 27. Goodness of fit statistics for AEGEAN pooled arms; Time to death as first EFS event (IA2)

Neoadjuvant PDC				
Model	**AIC**	**AIC Rank**	**BIC**	**BIC Rank**
Exponential	896.8	6	901.4	5
Weibull	892.8	5	902.0	6
Log-normal	883.7	3	892.9	3
Log-logistic	891.3	4	900.5	4
Gompertz	882.1	2	891.4	2
Generalised gamma	**875.7**	**1**	**889.5**	**1**

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Figure 22 shows the model fits for the pooled IA2 data across the AEGEAN arms.

Figure 22. EF to Death (TP3) model fits, pooled

Abbreviations: EFS, event-free; GPM, general population mortality; TP, transition probability

2.1.1.6 TP4 and TP5: Modelling from LRR and DM

The assumptions used to model transitions from subsequent health states, i.e., LRR and DM, remain unchanged from the original submission. The incorporation of the AEGEAN EFS IA2 data into the model did not require any update of the model inputs required to model TP4 and TP5.

In line with the NICE Committee's preferred base-case, an adjustment was made so that 60% of people eligible for immunotherapy treatment in the LRR and DM1 health states receives it. This contrasts to the original submission, whereby the model assumed that 70% (based on the NICE technology appraisal guidance durvalumab for maintenance treatment of unresectable NSCLC after platinum-based chemoradiation, TA798)[20] and 80% (based on TA683 and TA770)[21,22] of eligible people would receive immunotherapies at the LRR and DM1 states, respectively.

Table 28 to Table 31 show the distribution of patients in LRR, LRR (before and after weighting for BSC), DM1 and DM2, following the updates on the proportion of patients eligible for IO in LRR and DM1 (i.e., 60%).

Table 28. Distribution of patients LRR by treatment modality based on treatment at EF and IO restrictions

EF treatment	LRR treatment			
	CRT followed by durvalumab	RT	CRT	BSC
IO (no retreatment)	0.0%	14.3%	65.2%	20.5%
IO (retreatment)	31.8%	8.6%	39.1%	20.5%
No IO	31.8%	8.6%	39.1%	20.5%

EF treatment	LRR treatment			
	CRT followed by durvalumab	**RT**	**CRT**	**BSC**
Assumptions	NICE Committee preferred assumption and PD-L1≥1%	TA761 (ADAURA) assumed 18% RT and 82% CRT based on UK clinical expert opinion.[23] Same distribution used for those patients not receiving CRT followed by durvalumab[24] or BSC		Wong et al. 2016. % supportive care following local recurrence[25] No subsequent progression to DM

Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; DM, distant metastasis; IO, immuno-oncology; PD-L1, programmed cell death-ligand 1; RT, radiotherapy.

Table 29. Treatment shares for LRR treatment modalities before and after re-weighting

	No IO retreatment allowed	IO retreatment allowed	No IO
Treatment	**Share of treatment**		
CRT followed by durvalumab	0.0%	31.8%	31.8%
RT	14.3%	8.6%	8.6%
CRT	65.2%	39.1%	39.1%
Treatment	**Re-weighted (after removing the BSC proportion)**		
CRT followed by durvalumab	0.0%	40.0%	40.0%
RT	18.0%	10.8%	10.8%
CRT	82.0%	49.2%	49.2%

Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; IO, immuno-oncology; RT, radiotherapy.

Table 30. Distribution of patients in DM1 by treatment modality based on treatment in EF and IO restrictions

EF treatment	DM1 treatment							
	IO + CT (nsq) (Pembrolizumab + Carboplatin + Pemetrexed)	**IO + CT (sq)** (Pembrolizumab + Carboplatin + Paclitaxel)	**IO mono** (Pembrolizumab)	**IO mono** (Atezolizumab)	**IO + CT** (Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel)	**CT (nsq)** (Carboplatin + Pemetrexed)	**CT (sq)** (Carboplatin + Paclitaxel)	**BSC**
IO (no retreatment)	0.0%	0.0%	0.0%	0.0%	0.0%	39.2%	38.1%	22.7%
IO (retreatment)	13.1%	16.2%	11.8%	1.8%	3.5%	15.7%	15.2%	22.7%
No IO	13.1%	16.2%	11.8%	1.8%	3.5%	15.7%	15.2%	22.7%
Assumptions	IO+CT for patients receiving IO based on NICE Committee preferred assumption and PD-L1 <50% (based on IPSOS market shares for pembrolizumab/atezolizumab)	IO+CT for patients receiving IO based on NICE Committee preferred assumption and PD-L1 <50%	IO mono for patients receiving IO and PD-L1 ≥50% (based on IPSOS market shares for pembrolizumab/atezolizumab)		IO+CT for patients receiving IO based on NICE Committee preferred assumption and PD-L1 <50% (based on IPSOS market shares for pembrolizumab/ atezolizumab)	nsq patients not receiving IO	sq patients not receiving IO	Wong et al. 2016. % supportive care following distant recurrence [25]

Abbreviations: BSC, best supportive care; CT, chemotherapy; DM, distant metastasis IO, immuno-oncology; nsq, non-squamous; sq, squamous

Table 31. Distribution of patients in DM2 by treatment modality based on treatment at EF and IO restrictions

EF treatment	DM2 treatment		
	Atezolizumab	Docetaxel + Nintedanib	BSC
IO (no retreatment)	0.0%	55.4%	44.6%
IO (retreatment)	22.2%	33.2%	44.6%
No IO	22.2%	33.2%	44.6%
Assumptions	% BSC/no treatment for patients who received active treatment in DM1 and in line with the NICE Committee's preferred assumption on % on IO, based on 1-% patients receiving subsequent therapy in KEYNOTE trials (5-year) (pooled across treatment arms)[26-29]		

Abbreviations: BSC, best supportive care; DM2, distant metastases post-progression; EF, event-free; IO, immuno-oncology.

2.2 Health-related quality of life data used in the cost-effectiveness analysis

2.2.1 AEGEAN EFS IA2 Health-related quality of life data

At EFS IA2, there were additional EQ-5D observations compared to EFS IA1 (across both "pre-recurrence" and "post-recurrence"). In total, [redacted] EQ-5D-5L observations were available from [redacted] patients. Of these, [redacted] observations were recorded pre-recurrence, [redacted] were recorded post-recurrence and [redacted] were recorded after censoring for recurrence. The best fitting model in terms of AIC was the model including a term for *Recurrence status*.

The number of subjects, observations and mean estimates of the best fitting model are presented in Table 32. Similar to EFS in IA1, the pre-recurrence estimate across pooled treatment arms was used in the cost-effectiveness model to represent the EF health state utility. Since Treatment Status was not included in the best fitting model, the utilities applied in the model were specific to health-state rather than treatment-specific. Therefore, identical utilities were applied regardless of treatment received in each state, applicable for both AEGEAN and non-AEGEAN therapies.

Table 32. EQ-5D utility index (UK weights) – IA2

Treatment	Scenario	Subjects	Observations	Mean (SD)	Median (IQR)	Min	Max
Pooled treatments	Pre-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled treatments	Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IQR, interquartile range; SD, standard deviation; SoC, standard of care.

Utility values from AEGEAN were estimated for the EF health state. Utility values informing later health states (i.e., LRR, DM) remain unchanged from EFS IA1. An overview of the utilities used in the cost-effectiveness model is presented in Table 33.

Table 33. Summary of EF health state utility value – EFS IA2

Health state	Utility value	SE
EF	[redacted]	[redacted]

Abbreviations: EF, event-free; DM, distant metastasis; LRR, locoregional recurrence; PD, progressed disease; PF, progression-free; SE, standard error.

2.2.2 NICE-preferred utility assumption

The utility values from AEGEAN (IA2) used in the EF health state remained higher ([redacted]) than the age-adjusted utility value for the UK general population (0.829).[30] To align with the NICE Committee's preferred assumption to model utilities, the EF utility value was set to the age-matched utility from the general population for EF. Regarding the utility values in the subsequent health states, the EAG decrement scenario that the NICE Committee preferred was adopted. To be specific, a fixed decrement of 0.2 was used to generate the utility value for LRR, before generating utility values for DM1 and DM2, by maintaining the absolute decrements from the original base-case (LRR: [redacted], DM1: 0.759 and DM2: 0.662) and applying them to the modified LRR value (i.e. decrement from EF of 0.2 = 0.629).

Table 34. Summary of health state utility values

Health state	Utility value	SE	Notes
EF	0.829	0.005	Age-matched utility from the general population
LRR	0.629	0.062	EF utility and 0.2 decrement
DM1	[redacted]	[redacted]	LRR utility and original base-case LRR to DM1 decrement ([redacted] - 0.759 = [redacted])
DM2	[redacted]	[redacted]	LRR utility and original base-case LRR to DM2 decrement ([redacted] - 0.662 = [redacted])

Abbreviations: EF, event-free; DM, distant metastasis; LRR, locoregional recurrence; PD, progressed disease; PF, progression-free; SE, standard error.

2.3 Costs and healthcare resource use

2.3.1 Intervention and comparators' costs – Treatment acquisition cost for patients in EF health state

Neoadjuvant and adjuvant treatment costs for all therapies were calculated based on the time to discontinuation of treatment (TDT) data from AEGEAN EFS IA1 (DCO 10 November 2022) and IA2 (DCO 10 May 2024). The AEGEAN KM analysis of the mITT population consisted of (i) time to study treatment discontinuation or death (based on IA2) and (ii) time to neoadjuvant PDC treatment discontinuation or death (based on IA1). The updated KM plot for the time to study treatment discontinuation of perioperative durvalumab and perioperative placebo based on AEGEAN EFS IA2 (DCO 10 May 2024) is presented in Figure 23. The KM plot for (ii) time to neoadjuvant PDC treatment discontinuation or death (based on IA1) is presented in the original submission.

Figure 23. Time to treatment discontinuation of study treatment (KM Plot) – IA2

For outside-trial comparators, assumptions were made to model the TDT, in line with the original submission. All assumptions regarding modelling of TDT remain unchanged from the original submission.

2.4 Updated Cost-effectiveness Results

As requested by NICE, Table 35 presents an overview of the model adjustments and the resulting ICERs.

Table 35. Model adjustments following FAD comments

Scenario	Related FAD comment	Description adjustment	Justification adjustment	Model implementation adjustment	Incr. costs (£) perioperative durvalumab vs. neoadjuvant nivolumab	Incr. QALYs perioperative durvalumab vs. neoadjuvant nivolumab	ICER (£)perioperative durvalumab vs. neoadjuvant nivolumab	Cross reference
ACM company base-case	N/A	N/A	N/A	N/A	[redacted]	[redacted]	Dominant	N/A
1.1 - adjustment A*	Section 3.8	Assuming that transitions from the EF to the LRR and DM health states are split in line with the AEGEAN trial	The NICE committee concluded that it was more appropriate to model transitions out of EF based on the proportions seen in the AEGEAN trial, rather than the clinical expert figures, which according to them were based on historical experience without immunotherapies.	Update cells F94:G96 in the "Efficacy" tab with the proportions coming from the AEGEAN trial	[redacted]	[redacted]	Dominant	Section 2.1.1.4
1.2 - adjustment B*	Section 3.14	Assuming that 60% of people eligible for immunotherapy treatment in the LRR and DM1 health states will have it	The NICE committee considered the modelled proportions of eligible people for IO retreatment in subsequent stages too high, and thus, preferred to model 60% as eligible for IO retreatment in LRR and DM1.	Update cells K81:K82 in the "Settings" tab with the proportion preferred by the NICE Committee (i.e., 60%)	[redacted]	[redacted]	£1,818	Section 2.1.1.6
1.3 - adjustment C*	Section 3.16	EAG's decrement	The NICE committee considered it unrealistic that patients at the EF	Update cells E13, E20, E28:E29 in the "Utilities" tab with appropriate	[redacted]	[redacted]	Dominant	Section 2.2.2

		scenario to model utility	state would have a utility value higher than the general population. They also noted that the decrement in utility from EF to DM1 and DM2 was too small. The committee concluded that the EAG's decrement scenario to model utility was appropriate.	values per health state, to align with the EAG decrement scenario				
1.4 - adjustment D*	Section 3.17	Incorporation of updated data from AEGEAN EFS IA2 (DCO 10 May 2024)	The committee noted that further data from the AEGEAN trial would resolve some of the uncertainty in the model. Data from AEGEAN EFS IA2 (DCO 10 May 2024) have become available, hence, incorporated into the revised model.	Incorporation of updated EFS IA2 parameters, EFS IA2 KM data, updated NMA/MAIC HRs, IA2 safety and updated TDT data. The updates are found in the following tabs: "Efficacy Parameters", "Comparators' efficacy", "KM data (EFS & OS)" and "AEs".	[redacted]	[redacted]	£3,490	Sections 2.1-2.3
Revised company base-case	N/A	Use of NICE preferred assumptions and incorporation of updated AEGEAN data from EFS IA2 (DCO 10 May 2024)	To align with the NICE committee's preferred assumptions and request for updated trial data.	ACM COMPANY BASE-CASE + adjustments 1.1-1.4	[redacted]	[redacted]	£5,374	Section 2.4.1.1
***Adjustments 1.1-1.4 should be conditional on the "ACM COMPANY base-case"**								

Abbreviations: ACM, Appraisal Committee meeting; AE, adverse events; DCO, data cut-off; DM, distant metastasis; EAG, External Assessment Group; EFS, event-free survival; FAD, final appraisal determination; IA, interim analysis; IO, immuno-oncology; HR, hazard ratio; KM, Kaplan-Meier; LRR, locoregional recurrence; MAIC, matching-adjusted indirect comparison; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; TDT, time to discontinuation of treatment

2.4.1 Base-case results

The following section provides an overview of the base case results. Probabilistic sensitivity analysis outcomes, deterministic sensitivity analysis outcomes and outcomes from the scenario analyses are shown in Section 2.4.2.

[redacted]

2.4.1.1 Base-case incremental cost-effectiveness analysis deterministic results

The deterministic base case results following the incorporation of AEGEAN EFS IA2 data and NICE preferred assumptions are presented in Table 36 to Table 39. These results are based [redacted]. Per NICE guidelines, the results are presented as pairwise comparisons given that perioperative durvalumab is expected to replace the individual comparator therapies.

Table 40 presents the incremental deterministic net health benefit (NHB) per treatment versus perioperative durvalumab.[31]

Table 36. Base-case deterministic results: Perioperative durvalumab versus neoadjuvant PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£557

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 37. Base-case deterministic results: Perioperative durvalumab versus neoadjuvant nivolumab + PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,374

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 38. Base-case deterministic results: Perioperative durvalumab versus surgery alone

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Table 39. Base-case deterministic results: Perioperative durvalumab versus adjuvant PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,238

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 40. Net health benefit (deterministic base-case)

Perioperative durvalumab vs.	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Neoadjuvant PDC	[redacted]	[redacted]	1.83	1.79
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	0.83	0.69
Surgery alone	[redacted]	[redacted]	2.81	3.12
Adjuvant PDC	[redacted]	[redacted]	1.86	1.78

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years

2.4.2 Exploring uncertainty

2.4.2.1 Base-case incremental cost-effectiveness analysis probabilistic results

2.4.2.1.1 Probabilistic sensitivity analysis

In line with the original submission, a probabilistic sensitivity analysis (PSA) was performed using 1,000 simulations to assess the uncertainty of the results by varying parameters simultaneously according to statistical distributions using IA2 data.

Probabilistic results including total costs, life years gained (LYG), QALYs and incremental cost per QALY gained for perioperative durvalumab versus each comparator in the model are presented in Table 41 to Table 44. These results [redacted]. Per NICE guidelines, the results are presented as pairwise comparisons given that perioperative durvalumab is expected to replace the individual comparator treatment.

The NHB probabilistic base case results are presented in Table 45.

Table 41. Base-case probabilistic results: Perioperative durvalumab versus neoadjuvant PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,081

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 42. Base-case probabilistic results: Perioperative durvalumab versus neoadjuvant nivolumab + PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,943

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 43. Base-case probabilistic results: Perioperative durvalumab versus surgery only

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Surgery only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Table 44. Base-case probabilistic results: Perioperative durvalumab versus adjuvant PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,832

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 45. Net health benefit (probabilistic base-case)

Perioperative durvalumab vs.	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Neoadjuvant PDC	[redacted]	[redacted]	1.71	1.75
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	0.40	0.46
Surgery alone	[redacted]	[redacted]	3.25	3.11
Adjuvant PDC	[redacted]	[redacted]	1.73	1.79

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years

The results of the PSA are also presented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEAC). Pairwise comparisons in separate cost-effectiveness planes and separate CEACs are shown in Figure 24 to Figure 27 and Figure 28 to Figure 31, respectively. The CEAC of perioperative durvalumab against all comparators is shown in Figure 32.

Figure 24. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy; QALY, quality-adjusted life year

Figure 25. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant nivolumab + PDC

Abbreviations: PDC, platinum-doublet chemotherapy; QALY, quality-adjusted life year

Figure 26. Incremental cost effectiveness plane: perioperative durvalumab versus surgery alone

Abbreviations: QALY, quality-adjusted life year

Figure 27. Incremental cost effectiveness plane: perioperative durvalumab versus adjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy; QALY, quality-adjusted life year

Figure 28. CEAC: perioperative durvalumab versus neoadjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy

Figure 29. CEAC: perioperative durvalumab versus neoadjuvant nivolumab + PDC

Abbreviations: PDC, platinum-doublet chemotherapy

Figure 30. CEAC: perioperative durvalumab versus surgery alone

Figure 31. CEAC: perioperative durvalumab versus adjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy

Figure 32. CEAC: perioperative durvalumab versus all comparators

Abbreviations: PDC, platinum-doublet chemotherapy

2.4.2.2 Deterministic sensitivity analysis

The results from the updated OWSA following the incorporation of AEGEAN IA2 data and NICE preferred assumptions are presented in a tornado diagram for each pairwise comparison in Figure 33 to Figure 36. The tornado diagrams identify the top ten parameters which had the greatest impact on the ICER. In cases where a scenario led to any of the following outcomes: 'perioperative durvalumab dominated, 'perioperative durvalumab dominant,' or 'perioperative durvalumab is less costly and less effective,' the deterministic ICER is presented. For more details, please refer to Appendix A.

Figure 33. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; PF, progression-free disease; PD, progressed disease

Figure 34. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant nivolumab + PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; PF, progression-free disease; PD, progressed disease

Figure 35. Tornado diagram from OWSA - perioperative durvalumab vs. surgery alone

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; PF, progression-free disease; PD, progressed disease

Figure 36. Tornado diagram from OWSA - perioperative durvalumab vs. adjuvant PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; PF, progression-free disease; PD, progressed disease

2.4.2.3 Scenario analysis

Table 46 presents an overview and justification for each scenario.

Table 47 presents the scenario analysis results for perioperative durvalumab versus neoadjuvant nivolumab + PDC. Since NICE considered neoadjuvant nivolumab + PDC to be the only relevant comparator, scenario analysis was not conducted for the other comparators.

Across all scenarios tested, the results remained below the £20,000 per QALY range. The majority of scenarios resulted in ICERs below £10,000 per QALY. The two scenarios with the greatest impact were those when: (i) no IO re-treatment was applied and (ii) no cure was applied. This resulted in ICERs of £15,207 and £10,892, respectively, for perioperative durvalumab versus neoadjuvant nivolumab + PDC.

Table 46. Scenario analyses overview

Scenario nr.	Scenario	Base case parameter	Scenario parameter	Justification
1	Apply a warm-up period of 12 months starting from year 5	0	12	To assess the impact of using a warm-up period as per NICE TA876[32]
2	Apply cure at 6 years	5 years	6 years	To assess the impact of using an alternative cure scenario, whereby patients in both arms are considered cured after 6 years
3	No cure applied	Cure applied	No cure applied	To assess the impact of an extreme scenario whereby no cure is assumed.
4	Proportion of EFS non-death events being LRR using estimates based on clinical validation	[redacted]	[redacted]	Testing the impact of applying clinically validated figures, indicating that a higher proportion of patients will transition to DM, rather than LRR
5	EFS distribution for neoadjuvant PDC arm: log-logistic	Log-normal	Log-logistic	Testing the impact of using the best statistical fit for the PBO EFS KM curve
6	EFS distribution for neoadjuvant PDC arm: generalised gamma	Log-normal	Generalised gamma	Testing the impact of using the generalised gamma model for PBO EFS KM curve
7	EFS distribution for neoadjuvant PDC arm: Weibull	Log-normal	Weibull	Testing the impact of using the Weibull model for PBO EFS KM curve, which close to the committee preferred 5-year EFS in TA876[32]
8	EFS HR: applied to standard extrapolations (lognormal)	Piecewise extrapolation	Standard extrapolation (lognormal)	Test the impact of applying a single HR over time, instead of only post-surgery
9	EFS HR: applied to standard extrapolations (exponential)	Piecewise extrapolation	Standard extrapolation (exponential)	Test the impact of applying a single HR over time, instead of only post-surgery **- As requested by NICE in the clarification questions letter (Question B.11b)**
10	EFS HR: applied to standard extrapolations (generalized gamma)	Piecewise extrapolation	Standard extrapolation (generalised gamma)	Test the impact of applying a single HR over time, instead of only post-surgery - **As requested by NICE in the clarification questions letter (Question B.11b)**
11	No IO re-treatment permitted	6	481	Testing an extreme scenario whereby retreatment is not permitted.
12	Waiting period before IO retreatment: 12 months	6	12	Testing an alternative IO retreatment timepoint – **As requested by NICE in the clarification questions letter (Question B.18e)**
13	All eligible for IO patients receive IO retreatment post-recurrence (i.e., same distribution in all arms, as of no IO comparators)	IO in LRR: 0% IO in DM: 0%	IO: same as for non-IO comparators	Testing an alternative IO retreatment scenario – **As requested by NICE in the clarification questions letter (Question B.13c)**
14	Starting age at 70 years	70 years	64 years	Testing the impact of adopting the NICE Committee's preferred assumption
15	Mean EF utility from Andreas et al. 2018	AEGEAN	Andreas et al. 2018	Exploring the impact of using different utilities values i.e., from Andreas et al. 2018 in line with TA761 (EF=0.72, LRR=0.62, DM1=0.67, DM2= 0.51).[23,33]
16	Discounting costs/effects: 1.5%	3.5%	1.5%	Exploring the impact of a lower discount rate for cost or health effects (extreme scenario)

17	Vial sharing	No	Yes	Testing the impact of allowing for vial sharing – As requested by NICE in the clarification questions letter (Question B.23)
18	IO in DM1: 65.3% based on IO restrictions from EF and LRR health states	60.0%	65.3%	Testing the impact of adding IO restrictions from LRR and DM – As requested by NICE in the clarification questions letter (Question B.8)
19	Health state utility values from TA823	EF: 0.829 LRR: 0.629 DM1: [redacted] DM2:	EF (DFS in TA823): 0.80 LRR: 0.770 DM1: 0.710 DM2: 0.690	Exploring the impact of using different utility values i.e., from TA823[19] - **s requested by NICE in the clarification questions letter (Question B.16f)**
20	Health state utility values from TA761	EF: 0.829 LRR: 0.629 DM1: [redacted] DM2:	EF (DFS in TA761): [redacted] LRR: [redacted] DM1: [redacted] DM2: 0.640	Exploring the impact of using different utility values i.e., from TA761[23] - **As requested by NICE in the clarification questions letter (Question B.16b)** [a]
21	Type of surgery distribution based on TA876[32] - perioperative durvalumab same as neoadjuvant nivolumab + PDC	% Surgery: 80.6% Thoracotomy: 50% Minimally invasive: 50%	% Surgery: 83.2% Thoracotomy: 70.5% Minimally invasive: 29.5%	Based on TA876 (scenario tested for perioperative durvalumab vs. neoadjuvant nivolumab + PDC only)[32] - **As requested by NICE in the clarification questions letter (Question B.25b)**

Abbreviations: DM, distant metastasis; EFS, event-free survival; HR, hazard ratio; IO, immuno-oncology; IV, intravenous; LRR, locoregional recurrence; NICE, National Institute of Health and Care Excellence; NHS, National Health Service; PFS, progression-free survival; TA, technology appraisal; TTP, time to progression

Table 47. Scenario analyses results perioperative durvalumab versus neoadjuvant nivolumab + PDC

Scenario nr.	Scenario label	Perioperative durvalumab vs. neoadjuvant nivolumab + PDC			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
N/A	Base case	[redacted]	[redacted]	£5,374	-
1	Apply a warm-up period of 12 months starting from year 5	[redacted]	[redacted]	£4,668	-13.1%
2	Apply cure at 6 years for both arms	[redacted]	[redacted]	£5,308	-1.2%
3	No cure applied	[redacted]	[redacted]	£10,900	102.8%
4	Proportion of EFS non-death events being LRR using estimates based on clinical validation	[redacted]	[redacted]	£5,895	9.7%
5	EFS distribution for neoadjuvant PDC arm: log-logistic	[redacted]	[redacted]	£4,226	-21.4%
6	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	£5,558	3.4%
7	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	£3,945	-26.6%
8	EFS HR: applied to standard extrapolations (lognormal)	[redacted]	[redacted]	£1,165	-78.3%
9	EFS HR: applied to standard extrapolations (exponential)	[redacted]	[redacted]	£593	-89.0%
10	EFS HR: applied to standard extrapolations (generalized gamma)	[redacted]	[redacted]	£2,470	-54.0%
11	No IO re-treatment permitted	[redacted]	[redacted]	£15,207	183.0%
12	Waiting period before IO retreatment: 12 months	[redacted]	[redacted]	£8,928	66.1%
13	All eligible for IO patients receive IO retreatment post-recurrence (i.e., same distribution in all arms, as of no IO comparators)	[redacted]	[redacted]	£10,568	96.6%
14	Starting age at 70 years	[redacted]	[redacted]	£7,288	35.6%
15	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	£6,445	19.9%
16	Discounting costs/effects: 1.5%	[redacted]	[redacted]	£3,240	-39.7%
17	Vial sharing	[redacted]	[redacted]	£5,244	-2.4%
18	IO in DM1: 65.3% based on IO restrictions from EF and LRR health states	[redacted]	[redacted]	£4,804	-10.6%
19	Health state utility values from TA823	[redacted]	[redacted]	£6,054	12.7%
20	Health state utility values from TA761	[redacted]	[redacted]	£5,927	10.3%

21	Type of surgery distribution based on TA876[32] - perioperative durvalumab same as neoadjuvant nivolumab + PDC	[redacted]	[redacted]	£5,715	6.3%

Abbreviations: DM, distant metastasis; EFS, event-free survival; HR, hazard ratio; IO, immuno-oncology; IV, intravenous; LRR, locoregional recurrence; NICE, National Institute of Health and Care Excellence; NHS, National Health Service; PFS, progression-free survival; TA, technology appraisal; TTP, time to progression

2.4.2.3.1 Time-varying hazards - Scenario analysis

A separate scenario analysis using a time-varying HR approach has been conducted, as requested by the EAG and NICE committee. As detailed in Section 1.5, the log-normal model was used to obtain time-varying estimates of relative treatment effects from the MAIC and NMA.

For the time-varying HRs of perioperative durvalumab versus neoadjuvant PDC, the MAIC-adjusted time-varying estimates from the MAIC were considered in this scenario analysis across all comparisons. This is in line with the base-case using constant HRs (Section 2.1.1.2), since the main comparator for this submission is neoadjuvant nivolumab + PDC with the relative efficacy informed by the MAIC network.

Table 48 to Table 51 present the scenario analysis results for each comparator. These results are based [redacted]

Table 48. Time-varying hazards scenario results: Perioperative durvalumab versus neoadjuvant PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 49. Time-varying hazards scenario results: Perioperative durvalumab versus neoadjuvant nivolumab + PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

Table 50. Time-varying hazards scenario results: Perioperative durvalumab versus surgery alone

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Table 51. Time-varying hazards scenario results: Perioperative durvalumab versus adjuvant PDC

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£180

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; PDC, platinum-doublet chemotherapy; QALYs, quality-adjusted life years.

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Appendix A. Deterministic sensitivity analysis

The 5 parameters which had the largest impact on the ICER, along with their estimated ICERs, are shown in Table 52 to Table 55.

Table 52. DSA results – key model drivers (perioperative durvalumab vs. neoadjuvant PDC)

Parameter	Lower Bound Value	Base case value	Upper Bound value	Lower Bound	Base case	Upper Bound	Absolute difference
EFS: HR – Perioperative durvalumab vs. neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£1,818 [a]	£557	£21,908	£23,726
Discount rate - costs	0.02	0.04	0.06	-£930 [a]	£557	£1,940	£2,871
DM2 - Neoadjuvant PDC arm: No treatment/BSC market share	0.38	0.45	0.51	£14	£557	£1,046	£1,031
LRR - Neoadjuvant PDC arm: Durvalumab + Radiotherapy + Cisplatin + Etoposide market share	0.35	0.45	0.51	£972	£557	£156	£816
Drug cost - Surgery: % thoracotomy – Perioperative durvalumab arm	0.43	0.50	0.57	£198	£557	£917	£718

[a] Durvalumab dominant

Abbreviations: DM, distant metastasis; EFS, event-free survival; HR, hazard ratio; LRR, locoregional recurrence; PDC, platinum-doublet chemotherapy

Table 53. DSA results – key model drivers (perioperative durvalumab vs. neoadjuvant nivolumab + PDC)

Parameter	Lower Bound Value	Base case value	Upper Bound value	Lower Bound	Base case	Upper Bound	Absolute difference
EFS: HR - Neoadjuvant nivolumab + PDC vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£38,028 [b]	£5,374	-£3,484 [a]	£38,028
EFS: HR - Perioperative durvalumab vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£1,918 [a]	£5,374	-£15,086 [b]	£13,168
DM1 - Neoadjuvant nivolumab + PDC arm: No treatment/BSC market share (IO retreatment)	0.13	0.23	0.32	£2,687	£5,374	£7,899	£5,211
DM1 - Neoadjuvant nivolumab + PDC arm: Pembrolizumab market share (IO retreatment)	0.05	0.12	0.20	£7,055	£5,374	£3,206	£3,849
Time from last dose of neoadjuvant to first dose of adjuvant treatment (months)	2.26	2.76	3.34	£5,374	£5,374	£2,446	£2,928

[a] Durvalumab dominant

[b] Durvalumab dominated

Abbreviations: DM, distant metastasis; EFS, event-free survival; HR, hazard ratio; PDC, platinum-doublet chemotherapy

Table 54. DSA results – key model drivers (perioperative durvalumab vs. surgery alone)

Parameter	Lower Bound Value	Base case value	Upper Bound value	Lower Bound	Base case	Upper Bound	Absolute difference
EFS: HR - Surgery alone vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	£4,964	-£3,282 [a]	-£5,611 [a]	£10,575
EFS: HR - Perioperative durvalumab vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£4,053 [a]	-£3,282 [a]	-£270 [a]	£3,784
DM1 – Surgery alone arm: No treatment/BSC market share	0.12	0.23	0.33	-£5,150 [a]	-£3,282 [a]	-£1,391 [a]	£3,760
DM1 – Surgery alone arm: Pembrolizumab market share	0.04	0.12	0.21	-£2,118 [a]	-£3,282 [a]	-£4,813 [a]	£2,695
Discount rate - costs	0.02	0.04	0.06	-£4,660 [a]	-£3,282 [a]	-£1,993 [a]	£2,666

[a] Durvalumab dominant

Abbreviations: DM, distant metastasis; EFS, event-free survival; HR, hazard ratio; PDC, platinum-doublet chemotherapy

Table 55. DSA results – key model drivers (perioperative durvalumab vs. adjuvant PDC)

Parameter	Lower Bound Value	Base case value	Upper Bound value	Lower Bound	Base case	Upper Bound	Absolute difference
EFS: HR – Adjuvant PDC vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£60,757	£1,238 [b]	-£4,954 [a]	£55,804
EFS: HR - Perioperative durvalumab vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£1,345 [a]	£1,238	£23,089	£24,434
Discount rate - costs	0.02	0.04	0.06	£28	£1,238	£2,365	£2,337
DM1 - Adjuvant PDC arm: Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel (nsq) market share (No IO or retreatment)	0.01	0.04	0.09	£1,888	£1,238	£75	£1,813
DM1 - Adjuvant chemotherapy arm: Pembrolizumab + Carboplatin + Pemetrexed (nsq) market share (No IO or retreatment)	0.06	0.13	0.21	£2,055	£1,238	£249	£1,806

[a] Durvalumab dominant

[b] Durvalumab dominated

Abbreviations: DM, distant metastasis; EFS, event-free survival; HR, hazard ratio; PDC, platinum-doublet chemotherapy

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6220]

Draft guidance consultation – Additional evidence

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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1. Additional clinical evidence

1.1 AEGEAN Trial Interim Analysis 2 Results

The company have provided updated results from the trial i.e. data cut-off (DCO) 10 May 2024, updating the results summarised in the EAG report of DCO 10 November 2022.{AstraZeneca, 2024 [accessed 22.8.24] #266} Below is a brief summary.

1.1.1 Event free survival

Table 1.1: Event-free survival assessed by BICR per RECIST 1.1 at AEGEAN IA1 and IA2, mITT population

	IA1 (DCO 10 Nov 2022)		IA2 (DCO 10 May 2024)	
	Perioperative durvalumab (n=366)	**Perioperative placebo (n=374)**	**Perioperative durvalumab (n=366)**	**Perioperative placebo (n=374)**
Median EFS, months (95% CI)[a] EFS at 12 months, % (95% CI) EFS at 24 months, % (95% CI) EFS at 36 months, % (95% CI)	NR (31.9-NR) 73.4 (67.9-78.1) 63.3 (56.1-69.6) NR	25.9 (18.9-NR) 64.5 (58.8-69.6) 52.4 (45.4-59.0) NR	NR (42.3-NR) 73.3 (68.1-77.7) 65.0 (59.4-70.0) 60.1 (53.9-65.8)	30.0 (20.6-NR) 64.1 (58.7-69.0) 54.4 (48.7-59.6) 47.9 (41.8-53.8)
HR (95% CI)	0.68 (0.53-0.88)		0.69 (0.55-0.88)	

Based on Table 5, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

[a] Calculated using the Kaplan-Meier technique.

EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumours

EAG comment: The difference between the two DCOs is minimal overall, although the survival advantage is maintained at 36 months.

1.1.2 Disease free survival

These results were reported for the first time.

Table 1.2: Disease-free survival assessed by BICR per RECIST 1.1 at AEGEAN IA2, resected mITT population

	IA2 (DCO 10 May 2024)	
	Perioperative durvalumab (n=242)	**Perioperative placebo (n=231)**
Median DFS, months (95% CI)[a] DFS at 12 months, % (95% CI) DFS at 24 months, % (95% CI) DFS at 36 months, % (95% CI)	NR (NR-NR) 81.0 (75.2-85.5) 75.1 (68.7-80.4) 71.2 (63.8-77.3)	NR (41.5-NR) 74.1 (67.8-79.3) 62.4 (55.2-68.8) 61.4 (54.0-68.0)
HR (95% CI)	0.66 (0.47-0.92)	

Based on Table 6, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

[a] Calculated using the Kaplan-Meier technique.

DCO, data cut-off; DFS, disease-free survival; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumours

EAG comment: There is clear advantage to perioperative durvalumab, which is maintained at 36 months.

1.1.3 Overall survival

Table 1.3: Overall survival at AEGEAN IA1 and IA2, mITT population

	IA1 (10 Nov 2022)		IA2 (10 May 2024)	
	Perioperative durvalumab (n=366)	**Perioperative placebo (n=374)**	**Perioperative durvalumab (n=366)**	**Perioperative placebo (n=374)**
Median OS, months (95% CI)[a] OS at 12 months, % (95% CI) OS at 24 months, % (95% CI) OS at 36 months, % (95% CI)	NR (NR-NR) 83.6 (79.2-87.2) 71.7 (65.2-77.2) NR	NR (NR-NR) 85.9 (81.7-89.1) 72.0 (65.5-77.5) NR	NR (NR-NR) 84.3 (80.1-87.7) 74.4 (69.5-78.6) 67.1 (61.6-71.9)	53.2 (44.3-NR) 85.3 (81.2-88.5) 72.2 (67.3-76.5) 63.9 (58.4-69.0)
HR (95% CI)	1.02 (0.75-1.39)		0.89 (0.70-1.14)	

Based on Table 7, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

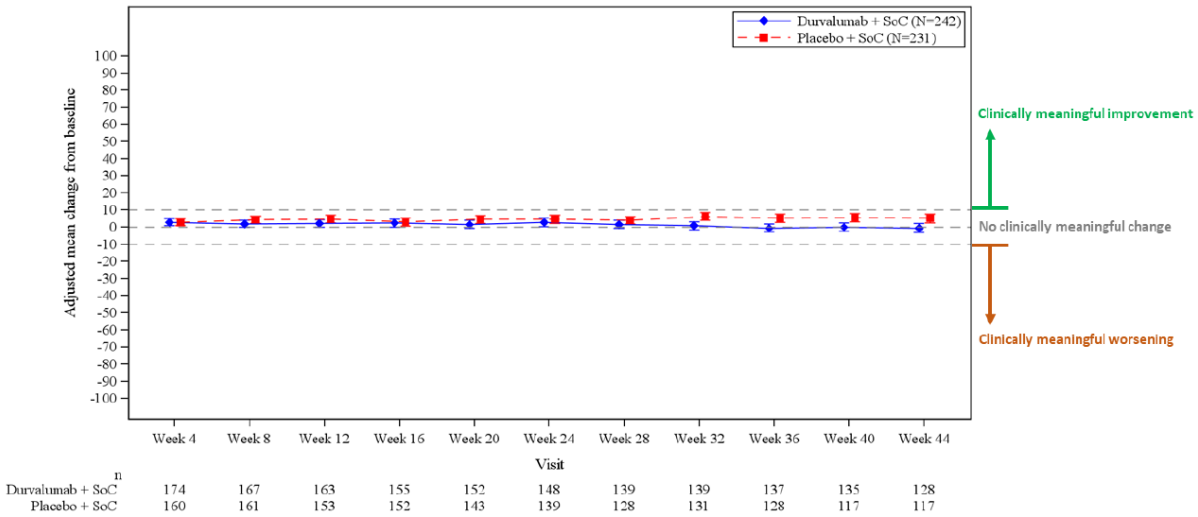
[a] Calculated using the Kaplan-Meier technique.

EFS, event-free survival; HR, hazard ratio; mITT, modified intent-to-treat; NR, not reached; RECIST, Response Evaluation Criteria in Solid Tumours

EAG comment: There continues to be little difference between the two arms of the AEGEAN trial, the numerical advantage appearing to shift towards perioperative durvalumab.

1.1.4 Health related quality of life

Figure 1.1: Adjusted mean change from adjuvant baseline in EORTC QLQ-C30 scores by MMRM analysis at AEGEAN IA2, resected mITT population



Based on Figure 3, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

Note: Durvalumab and placebo refer to the perioperative durvalumab and the perioperative placebo arms in AEGEAN. Circles indicate censored observations.

CI, confidence interval; DCO, data cut-off; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; mITT, modified intention to treat; NR, not reached

EAG comment: Updated EORTC QLQ-C30 data continued to show no clinically meaningful difference between the durvalumab and the placebo arms, although after week 4 and until the latest follow-up of week 44, the values for the placebo arm showed a slight advantage.

1.1.5 Adverse events

Table 1.4: Adverse events

	IA1 (10 Nov 2022)		IA2 (10 May 2024)	
Overall study period	**Perioperative durvalumab (n=401)**	**Perioperative placebo (n=398)**	**Perioperative durvalumab (n=401)**	**Perioperative placebo (n=398)**
AEs of any grade and any cause	**387 (96.5)**	**377 (94.7)**	**387 (96.5)**	**379 (95.2)**
Maximum grade 3 or 4	170 (42.4)	172 (43.2)	175 (43.6)	172 (43.2)
SAEs	151 (37.7)	125 (31.4)	157 (39.2)	126 (31.4)
Events leading to death	23 (5.7)	15 (3.8)	23 (5.7)	15 (3.8)
Leading to discontinuation of durvalumab or placebo	48 (12.0)	24 (6.0)	51 (12.7)	25 (6.3)
Leading to cancellation of surgery	7 (1.7)	4 (1.0)	7 (1.7)	4 (1.0)
AEs of any grade possibly related to durvalumab, placebo or chemotherapy, n (%)	**348 (86.8)**	**321 (80.7)**	**350 (87.3)**	**325 (81.7)**
Maximum grade 3 or 4	130 (32.4)	131 (32.9)	134 (33.4)	133 (33.4)
Events leading to death[b]	7 (1.7)	2 (0.5)	7 (1.7)	2 (0.5)

	IA1 (10 Nov 2022)		IA2 (10 May 2024)	
Overall study period	**Perioperative durvalumab (n=401)**	**Perioperative placebo (n=398)**	**Perioperative durvalumab (n=401)**	**Perioperative placebo (n=398)**
Any immune-related AE	**95 (23.7)**	**37 (9.3)**	**104 (25.4)**	**41 (10.3)**
Any grade 3 or 4	17 (4.2)	10 (2.5)	18 (4.5)	10 (2.5)

Based on Table 24, CS[1] and Table 8, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}
[a]The safety analysis set includes all patients who underwent randomisation and received at least one dose of trial treatment or placebo; one patient assigned to the placebo group erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the durvalumab group for the safety analysis set. Safety data is shown for the overall trial period, which spans the time from the first dose of any trial treatment or placebo until the earliest of the last dose of any trial treatment or placebo or surgery + 90 days, the DCO date, or the date of the first dose of subsequent anti-cancer treatment.
[b]AEs with an outcome of death included deaths assessed by the investigator as possibly related to any systemic trial treatment and include interstitial lung disease (in two patients) and immune-mediated lung disease, pneumonitis, haemoptysis, myocarditis, and decreased appetite (one patient each) in the durvalumab group and pneumonia and infection (one patient each) in the perioperative placebo group.
AE = adverse events; CS = company submission; DCO = data cut-off; SAEs = serious adverse events

EAG comment: The difference between the two DCOs in the summary statistics appears to be minimal.

1.2 Updated Match-Adjusted Indirect Comparison Results

Due to the availability of new data for both trials, the MAIC has been updated using AEGEAN EFS data from IA2 (DCO 10 May 2024) (stratified HR 0.69 at IA2 versus 0.68 at IA1 (DCO 10 November 2022) – see Section 1.1) and the 4-year results for CheckMate 816 (HR 0.66 at 4-year update vs 0.68 at 3-year update).

The methods remained the same except for the addition of only ECOG PS instead of ECOC PS + age in the clarification letter in the second scenario.

A summary is shown in the table below. In conclusion, results of the MAIC were largely unchanged between EFS IA1 and IA2 analyses.

EAG comment: The differences between the original and updated analyses appear to be small.

Table 1.5: MAIC EFS HRs for the overall trial period comparing perioperative durvalumab versus neoadjuvant nivolumab + PDC (unweighted and after weighting in the base case and scenario analyses)

		Original CS			Update		
Comparison	**Scenario**	**EFS HR**	**LCL (95%)**	**UCL (95%)**	**EFS HR**	**LCL (95%)**	**UCL (95%)**
Perioperative durvalumab versus neoadjuvant nivolumab + PDC	Unweighted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 2[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 20, CS[1] and Table 13, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}
Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18[2] planned platinum chemotherapy, PD-L1 expression, region, stage, histology, sex and smoking status
Scenario 1 = weighting based on possible effect modifiers that are imbalanced between trials: planned platinum chemotherapy, PD-L1 expression, region, and stage
Scenario 2 = weighting based on base case plus [a]ECOG + age in CS, ECOG only for in Additional evidence.
Abbreviations: EFS, event-free survival; HR, hazard ratio; LCL, lower control limit; PDC, platinum-doublet chemotherapy; UCL upper control limit

Table 1.6: MAIC piecewise EFS HRs (0-to-3-months and 3+ month time intervals) for perioperative durvalumab versus neoadjuvant nivolumab + PDC

Comparison	Scenario	Original CS and clarification letter						Additional evidence					
		0–3 m time interval			3+ m time interval			0–3 m time interval			3+ m time interval		
		EFS HR	LCL (95%)	UCL (95%)	EFS HR	LCL (95%)	UCL (95%)	EFS HR	LCL (95%)	UCL (95%)	EFS HR	LCL (95%)	UCL (95%)
Perioperative durvalumab versus neoadjuvant nivolumab + PDC	Unweighted	[redacted]											
	Base case	[redacted]											
	Scenario 1	[redacted]											
	Scenario 2	[redacted]											

Based on Table 14, company response to clarification[3] and Table 14, Additional Evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}
Base-case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18: planned platinum chemotherapy, PD-L1 expression, region, stage, histology, sex and smoking status
Scenario 1 = weighting based on possible effect modifiers that are imbalanced between trials: planned platinum chemotherapy, PD-L1 expression, region, and stage.
Scenario 2 = weighting based on base case plus [a]ECOG + age in CS, ECOG only for in Additional evidence.
CS = company submission; DSU = Decision Support Unit; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; HR = hazard ratio; LCL = lower confidence limit; m = month; MAIC = matching adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed cell death ligand-1; PDC = platinum-doublet chemotherapy; PS = Performance Status; TSD = Technical Support Document; UCL = upper confidence limit

1.3 Updated Network-Meta Analysis Results

The NMA was also updated to include EFS data from the IA2 of AEGEAN (DCO 10 May 2024; mITT population).

The methods remained the same.

Results were presented for analyses of the same form as in the original CS i.e. base case and three scenario analyses. Only those for Scenario analysis 2 are presented here because of the general similarity between the original and the update and because the EAG agreed with the choice of this scenario for the CEA.

Figure 1.2: Original analysis: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 2)

Based on Figure 17, CS[1]
Sensitivity analysis 2 = excludes Rosell 1994, Li 2009 (studies with stage III patients only)
CrI = credible interval; CS = company submission; EFS = event-free survival; HR = hazard ratio; mITT = modified intention-to-treat; PDC = platinum-doublet chemotherapy

Figure 1.3: Updated analysis: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 2)

Based on Figure 7, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}
Sensitivity analysis 2 = excludes Rosell 1994, Li 2009 (studies with stage III patients only)
CrI = credible interval; CS = company submission; EFS = event-free survival; HR = hazard ratio; mITT = modified intention-to-treat; PDC = platinum-doublet chemotherapy

1.4 Multilevel Network Meta-Regression Feasibility Assessment

The company concluded that such an analysis was infeasible because: *"…it is reliant on the strong assumption of shared effect modification, which is invalid for this network due to the clinical implausibility of the assumption (varying treatment classes and regimens)."* (p. 22)

EAG comment: The EAG agrees that shared effect modification is probably a strong assumption given the variation in treatment class and some evidence from subgroup analyses of inconsistent variation in treatment effect. However, this must be weighed against the limitation of the use of two different methods of evidence synthesis, one for the comparison with neoadjuvant nivolumab and another for the comparison with all other comparators. As the EAG stated in the EAG report: *"Given that the MAIC adjusts the HR for durvalumab + neoadjuvant PDC versus neoadjuvant PDC and, via the ITC, versus neoadjuvant nivolumab + neoadjuvant PDC, to better match the CheckMate 816 trial population, these HRs can no longer be compatible with the AEGEAN trial population. However, no population adjustment is made for comparisons with adjuvant PDC or surgery, which are via the NMA. The MAIC demonstrates that the HR does change and so it seems likely that all treatment effects would be affected by the population characteristics."* (p. 26)

1.5 Time-Varying Hazards Analysis

Following requests by the EAG and NICE committee, a time-varying hazard ratio (HR) approach, using methods described by Cope et al. 2020,[4] was employed for the EFS analyses described in Sections 1.2 and 1.3. A fixed effects model was chosen due to: *"…the limited evidence base and lack of a plausible (weakly informative) prior for the between-study heterogeneity terms, the 95% CrIs were too wide to be of use."* (p. 23)

1.5.1 Results for MAIC versus neoadjuvant nivolumab

According to the Akaki Information Criterion (AIC), the Gompertz model produced the best fit to the Kaplan-Meier (K-M) data for all four arms of the two trials, except for the nivolumab arm of the CheckMate 816 trial where it was the log-normal. The company also stated that the Gompertz produced the best visual fit. However, the log-normal was chosen because it was: *"…the second best-fitting distribution, allows for more flexibility in terms of arc-shaped hazards."* (p. 23) A figure comparing the HRs of perioperative durvalumab vs neoadjuvant nivolumab over time for each of the parametric models and one comparing the log-normal to the stratified proportional hazards (PH) analysis are shown below.

Figure 1.4: EFS hazard ratios for perioperative durvalumab vs neoadjuvant nivolumab over time – fixed effect model

Based on Figure 12, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

Figure 1.5: EFS HR over time for perioperative durvalumab vs neoadjuvant nivolumab, fixed effect model (log-normal)

Based on Figure 13, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

EAG comment: The Gompertz model would seem to be the best choice in terms of statistical and visual fit. However, Figure 1.3 shows that the HR for perioperative durvalumab vs neoadjuvant nivolumab would decrease in a linear relationship with time, which appears to be implausible. Because of that implausibility, the log-normal does seem to be a reasonable choice.

1.5.2 Results for NMA versus adjuvant PDC, neoadjuvant PDC and surgery alone

[redacted]

According to the AIC, the lognormal, followed by the Gompertz model, produced the best fit to the K-M data for most (n=6 and 4 respectively) of the 11 arms of the five trials. The company stated that *"Based on an assessment of the statistical and visual fit across all the treatments in the different trials, the log-normal distribution was considered to provide the best fit."* (p.26) A figure comparing the HRs of perioperative durvalumab vs each of the comparators in the NMA over time for each of the parametric models and one comparing the log-normal to the stratified PH analysis are shown below.

Figure 1.6: EFS hazard ratios for perioperative durvalumab vs comparators over time – fixed effect model

[redacted]

Based on Figure 16, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

Figure 1.7: EFS HR over time for perioperative durvalumab vs comparators, fixed effect model (log-normal)

Based on Figure 17, Additional evidence.{AstraZeneca, 2024 [accessed 22.8.24] #266}

EAG comment: It appears that in most cases the visual fit of the log-normal is at least as good as that of the other parametric models. Given that, and the generally good statistical fit, the company's choice of the log-normal seems reasonable.

2. Additional Economic Evidence and Updated Cost-Effectiveness Results

2.1 Summary of company's changes compared with the ACM 1 company base-case

The company provided an instructive overview (Company response Table 35) listing the company's changes compared with the ACM 1 company base-case (with appropriate details). Compared with the ACM 1 company base-case, the company's response includes updates for:

1. Assuming that transitions from the EF to the LRR and DM health states are split in line with the AEGEAN trial
2. Assuming that 60% of people eligible for immunotherapy treatment in the LRR and DM1 health states will have it
3. EAG's decrement scenario to model utility
4. Incorporation of updated data from AEGEAN EFS IA2 (DCO 10 May 2024)

The estimated probabilistic ICERs (with PAS) for the original CS base-case, ACM 1 CS base-case and current CS base-case were £23,625, £24,016 and £5,943 per QALY gained respectively, for perioperative durvalumab versus neoadjuvant nivolumab + PDC. The original EAG base-case ICER range (with PAS) for perioperative durvalumab versus neoadjuvant nivolumab + PDC was £24,177 to £30,694 per QALY gained (Table 2.1).

Table 2.1: Cost effectiveness results including PAS

Technology	Total			Incremental (versus durvalumab)			ICER (£/QALY)	iNHB at £20,000	iNHB at £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
CS company base-case (probabilistic)									
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,194	1.16	1.33
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,625	-0.12	0.14
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	2.72	2.69
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,872	1.36	1.50
ACM 1 company base-case (probabilistic)									
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,151	1.14	1.31
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,016	-0.13	0.13
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	2.69	2.65
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,770	1.24	1.41
Updated company base-case post ACM 1 (probabilistic)									
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,081	1.71	1.75
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,943	0.40	0.46
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	3.25	3.11
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,832	1.73	1.79
EAG base-case (probabilistic): Cure applied									
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Technology	Total			Incremental (versus durvalumab)			ICER (£/QALY)	iNHB at £20,000	iNHB at £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,181	1.12	1.29
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,177	-0.13	0.13
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£958	2.66	2.62
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,871	1.23	1.40
EAG base-case (probabilistic): No cure applied									
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,628	0.62	0.98
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,694	-0.35	-0.02
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,735	1.85	2.10
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,635	0.65	1.02

ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; LY = life years; PDC = platinum-doublet chemotherapy; QALY = quality-adjusted life year

2.1.1 Reproducing company's updated base-case

The EAG used the ACM 1 company base-case (deterministic ICER perioperative durvalumab vs neoadjuvant nivolumab + PDC: £19,897, model file: "ID6220_Durvalumab_Cost Effectiveness Model_Final CON_14MAR2024[CON].xlsm") to reproduce the company's updated base-case by implementing the changes highlighted above. Notably, when implementing adjustment 1.4 alone, the EAG could not reproduce the ICER of £3,490 for perioperative durvalumab versus neoadjuvant nivolumab as presented in Additional Evidence document Table 35.{AstraZeneca, 2024 [accessed 22.8.24] #266} The EAG instead produced an ICER of £3,458 (incremental costs were within £1 of those reported and incremental QALYs were reproducible). However, when running the updated base case with adjustments 1.1-1.4 all implemented, the EAG could reproduce all incremental QALYs, and all incremental costs and ICERs within £1. The minor differences in costs and ICERs are likely due to rounding.

2.2 EAG comments

2.2.1 Adjustment 1: Assuming that transitions from the EF to the LRR and DM health states are split in line with the AEGEAN trial

The probability of the non-death EFS event being LRR or DM was estimated to be [redacted] and [redacted] respectively based on the AEGEAN trial. However, based on clinical opinion, indicating a greater proportion of patients transition to the DM state, the original CS base-case assumes this distribution to be [redacted] and [redacted] for LRR and DM respectively. These proportions were assumed to be constant over time and treatment independent.

The NICE committee concluded that the base-case should include the AEGEAN trial analysis data on the site of recurrence, rather than the figures validated by clinical experts. Hence, the updated company base-case now includes the NICE committee preferred assumption (ACM 3.8).

EAG comment: The EAG believes this adjustment is reasonable.

2.2.2 Adjustment 2: Assuming that 60% of people eligible for immunotherapy treatment in the LRR and DM1 health states will have it

The original CS base-case assumed that 70% will receive immunotherapy if immunotherapy is permitted and PD-L1 ≥1% in the LRR health state while it is assumed that 80% will receive immunotherapy if immunotherapy is permitted in the DM1 health state (EAG report Table 4.6).

The company lowered these immunotherapy retreatment percentages to 60% for people eligible for immunotherapy treatment in the LRR and DM1 health states. This is in line with the NICE Committee's preferred base-case (ACM 3.14).

EAG comment: The EAG believes this adjustment is reasonable.

2.2.3 Adjustment 3: EAG's decrement scenario to model utility

In the original CS, utilities were informed by the AEGEAN trial for EF, the PACIFIC for LRR, and KEYNOTE-189 for DM health states. With this approach, EF utility was above the age-matched utility value for the general population (0.829) and, as highlighted by the EAG, utility decrements to subsequent health states were small.

To align with the EAG's decrement scenario and the committee's preference (see ACM 3.16), the company capped the EF utility and the age-matched value for the general population. A fixed decrement of 0.2 was utilised to derive LRR utility. DM1 and DM2 utilities were derived through maintaining the absolute decrements from the original CS base case.

EAG comment: The EAG believes this adjustment is reasonable.

2.2.4 Adjustment 4: Incorporation of updated data from AEGEAN EFS IA2

The company's updated base-case informed EFS using AEGEAN interim analysis 2 (IA2; DCO 10 May 2024). Specifically, the company updated estimated EFS, OS, relative effectiveness for EFS, adverse event occurence and time to discontinuation of treatment. This aligns with committee preferences as the Draft guidance consultation noted: {National Institute for Health and Care Excellence, 2024 [accessed 23.7.24] #267} "*The committee noted that additional evidence from AEGEAN, if it were to become available, might reduce some of the uncertainty in the clinical evidence*".

The company indicated that, overall, the EFS results at IA2 were consistent with the IA1 results. The procedure to select the EFS (extrapolation) approach, used by the company, resulted in the KM + log-normal parametric distribution (consistently with the original CS base-case), was reasonable according to the EAG. See Tables 20 and 21 in the company's response for the predicted EFS and OS using standard parametric models.

Similar to the original CS base-case approach, the EFS for strategies other than neoadjuvant PDC were estimated by applying a HR to the neoadjuvant PDC EFS from month 3 onwards (Table 2.2). These were updated using AI2 data, resulting in very similar HRs compared with the original CS base-case (see EAG report Table 4.5).

Table 2.2: EFS piecewise (3 + months) HRs

	HR (95% CI) versus neoadjuvant PDC	Method
Perioperative durvalumab	[redacted]	MAIC weighting to CheckMate-816
Neoadjuvant nivolumab + PDC	[redacted]	MAIC weighting to CheckMate-816
Surgery alone	[redacted]	Random effects NMA
Adjuvant PDC	[redacted]	Random effects NMA
CI = confidence interval; CS = company submission; EFS = event-free survival; HRs = hazard ratios; PDC = platinum-doublet chemotherapy; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis		

Time to treatment discontinuation (TDT) was updated based on AI2 data. However, the company stated that all assumptions regarding modelling of TDT remain unchanged.

EAG comment: The EAG believes this adjustment is reasonable.

2.2.5 Company's sensitivity and scenario analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

The following issues mentioned in the ACM were explored by the company in scenario analyses:

- Starting age of the model should be set to 70 years in line with the likely NHS clinical practice population (ACM 3.7)
    - Scenario 14 - Starting age at 70 years
- 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 (ACM 3.9).
    - Section 2.4.2.3.1 - Time-varying hazards scenario
- 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 (ACM 3.15).
    - Scenario 1 - Apply a warm-up period of 12 months starting from year 5
    - Scenario 2 - Apply cure at 6 years for both arms
    - Scenario 3 - No cure applied

The parameters that have the greatest effect on the ICER (based on the company's DSA) are:

- EFS HRs
- Discount rates for costs and effects
- Immunotherapy retreatment market share

Scenario analyses indicated that the following modelling assumptions had the greatest upward effect on the ICER (comparison: perioperative durvalumab versus neoadjuvant nivolumab + PDC):

1. No IO re-treatment permitted
2. No cure applied
3. All eligible for IO patients receive IO retreatment post-recurrence (i.e., same distribution in all arms, as of no IO comparators)
4. Waiting period before IO retreatment: 12 months
5. Starting age at 70 years

2.3 EAG proposed additional analyses

The Draft guidance consultation indicated additional treatment effect waning should be explored in scenarios without a cure assumption: {National Institute for Health and Care Excellence, 2024 [accessed 23.7.24] #267}

> "*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*" (Section 3.10).

Additionally, the Draft guidance consultation indicated uncertainty related to the relative effectiveness of immunotherapy retreatment:{National Institute for Health and Care Excellence, 2024 [accessed 23.7.24] #267}

> "*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*" (Section 3.14).
>
> "*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*" (Section 3.14).

Given the above, additional scenario analyses exploring the impact of treatment effect waning (when no cure is assumed) as well as the relative effectiveness of immunotherapy retreatment might be informative.

3. References

[1] AstraZeneca. *Durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6220]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*, 2024 [accessed 19.2.24]

[2] Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. *NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. Technical Support Documents. NICE Decision Support Unit*, 2016

[3] National Institute for Health and Care Excellence. *Durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6220]: Response to request for clarification from the EAG*, 2024 [accessed 15.3.24]

[4] Cope S, Chan K, Jansen JP. Multivariate network meta-analysis of survival function parameters. Res Synth Methods 2020; 11(3):443-56

Single Technology Appraisal

Durvalumab with chemotherapy before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating resectable non-small-cell lung cancer [ID6220]

EAG critique of company's additional evidence (draft guidance consultation) – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG's critique of the company's additional evidence received at the draft guidance consultation stage, to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **4pm on Friday 30 August 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[redacted]	[redacted]	The current ICERs do not reflect the true cost effectiveness of perioperative durvalumab versus neoadjuvant nivolumab.	Not a factual error. The aim of Section 2.1 of the EAG's critique of the additional evidence was to clarify the history of this appraisal [redacted] ICERs are consistent as reported in the original EAG report, the CS base-case, the CS addendum for ACM 1 and their latest addendum).

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment
Give full details of inaccuracy found including page number in EAG report	Give details of any corrections that should be made	[redacted]

Issue 3

Description of problem	**Description of proposed amendment**	**Justification for amendment**
Give full details of inaccuracy found including page number in EAG report	Give details of any corrections that should be made	[redacted]

(please cut and paste further tables as necessary)

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	[redacted]

(Please add further lines to the table as necessary)