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

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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:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Astrazeneca:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Appendix

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Roy Castle Lung Cancer Foundation

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts**
   a. Patient expert – nominated by NICE

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

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Single technology appraisal

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

Document B

Company evidence submission

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Contents

Tables and figures 5
Abbreviations 10
B.1. Decision problem, description of the technology and clinical care pathway 13
B.1.1 Decision problem 14
B.1.2 Description of the technology being evaluated 18
B.1.3 Health condition and position of the technology in the treatment pathway 19
B.1.3.1 Disease overview 19
B.1.3.2 Burden to patients and society 20
B.1.3.3 Clinical pathway of care 21
B.1.3.4 Unmet need for resectable NSCLC in the UK 23
B.1.3.5 Proposed place of perioperative durvalumab in the clinical care pathway for resectable NSCLC in the UK 25
B.1.4 Equality considerations 26
B.2. Clinical effectiveness 27
B.2.1 Identification and selection of relevant studies 28
B.2.2 List of relevant clinical effectiveness evidence 29
B.2.3 AEGEAN 32
B.2.3.1 Summary of methods 32
B.2.3.2 Patient disposition 39
B.2.3.3 Patient baseline characteristics 41
B.2.4 Statistical analysis and definition of study groups 43
B.2.4.1 Definition of study groups 43
B.2.4.2 Statistical analysis 44
B.2.5 Critical appraisal of AEGEAN 46
B.2.6 Clinical effectiveness results 47
B.2.6.1 Primary outcome: EFS 47
B.2.6.2 Primary outcome: pCR 50
B.2.6.3 Key secondary outcomes 51
B.2.6.4 Health-related quality of life 55
B.2.6.5 Surgical outcomes 56
B.2.7 Subgroup analysis 57
B.2.7.1 Subgroup analysis for EFS 57
B.2.7.2 Subgroup analysis for pCR 59
B.2.8 Meta-analysis 60
B.2.9 Indirect and mixed treatment comparisons 60
B.2.9.1 MAIC versus neoadjuvant nivolumab 60
B.2.9.2 NMA versus adjuvant PDC and surgery alone 64
B.2.10 Adverse reactions 70

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B.2.10.1 Exposure 70
B.2.10.2 Adverse event overview 71
B.2.11 Ongoing studies 77
B.2.12 Interpretation of clinical effectiveness and safety evidence 77
B.2.12.1 Principal findings from the clinical evidence for perioperative durvalumab 77
B.2.12.2 Strengths of the evidence base 78
B.2.12.3 Potential limitations 79
B.2.12.4 Conclusions on the clinical effectiveness of perioperative durvalumab . 81
B.3. Cost effectiveness 83
B.3.1 Published cost-effectiveness studies 84
B.3.1.1 Identification of studies 84
B.3.1.2 Description of identified studies 84
B.3.1.3 Quality assessment of identified studies 89
B.3.2 Economic analysis 89
B.3.2.1 Patient population 91
B.3.2.2 Model structure 92
B.3.2.3 Intervention technology and comparators 93
B.3.3 Clinical parameters and variables 94
B.3.3.1 Modelling event-free health state 94
Neoadjuvant nivolumab + PDC (CheckMate-816) 108
Surgery alone and adjuvant PDC 108
B.3.3.2 Estimation of transition probabilities for competing events 109
B.3.3.3 Modelling of EFS (TP1, TP2 andTP3) 109
B.3.3.4 Modelling from locoregional recurrence (LRR) (TP4 and TP5) 113
B.3.3.5 Modelling of Distant Metastases (TP6) 119
B.3.4 Measurement and valuation of health effects 126
B.3.4.1 Health-related quality-of-life data from clinical trials 126
B.3.4.2 Health-related quality-of-life studies 128
B.3.4.3 Health-related quality of life data used in the cost-effectiveness analysis 128
B.3.4.4 Adverse reactions 129
B.3.4.5 Age adjustment 129
B.3.5 Cost and healthcare resource use identification, measurement and valuation 130
B.3.5.1 Resource identification, measurement and valuation studies 131
B.3.5.2 Intervention and comparators' costs and resource use 131
B.3.5.3 Subsequent health-state unit costs 141
B.3.5.4 Treatment monitoring costs 150

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B.3.5.5 Healthcare resource use and costs 150
B.3.5.6 Adverse reaction unit costs and resource use 153
B.3.6 Managed access proposal 153
B.3.7 Summary of base-case analysis inputs and assumptions 154
B.3.7.1 Summary of base-case analysis inputs 154
B.3.7.2 Assumptions 157
B.3.8 Base-case results 160
B.3.8.1 Base-case incremental cost-effectiveness analysis deterministic results 160
B.3.8.2 Clinical outcomes from the model 163
B.3.9 Exploring uncertainty 163
B.3.9.1 Base-case incremental cost-effectiveness analysis probabilistic results 163
B.3.9.2 Deterministic sensitivity analysis 168
B.3.9.3 Scenario analysis 170
B.3.10 Benefits not captured in the QALY calculation 176
B.3.11 Subgroup analysis 176
B.3.12 Validation 176
B.3.12.1 Validation of cost-effectiveness analysis 176
B.3.12.2 Validation with external clinical experts 177
B.3.13 Interpretation and conclusions of economic evidence 177
B.4. References 179

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Tables and figures

List of Tables

Table 1. The decision problem 15
Table 2. Technology being evaluated 18
Table 3. List of relevant clinical evidence 30
Table 4. Clinical effectiveness evidence 31
Table 5. Summary of AEGEAN methodology 33
Table 6. Key eligibility criteria for AEGEAN 38
Table 7. Patient disposition in AEGEAN at EFS first interim analysis, mITT population 39
Table 8. Patient disposition in AEGEAN at pCR first interim analysis, mITT population 40
Table 9. Patient disposition at D120SU 40
Table 10. Number of cycles and completion of planned treatment at D120SU 41
Table 11. Key patient demographics and baseline characteristics in AEGEAN 42
Table 12. Key disease characteristics in AEGEAN 43
Table 13. Study group definitions in AEGEAN 44
Table 14. Quality assessment results for AEGEAN 46
Table 15. OS HR at D120SU 52
Table 16. ORR prior to surgery (BICR RECIST v1.1), mITT population 55
Table 17. Summary of surgical outcomes, mITT population 56
Table 18. ESS of AEGEAN (weighted to match CheckMate 816) in the base case and scenario 1 62
Table 19. Cox regression analysis of EFS for perioperative durvalumab versus perioperative placebo in AEGEAN (unweighted and after weighting in the base case and scenario 1) 62
Table 20. MAIC EFS HRs for perioperative durvalumab versus neoadjuvant nivolumab + PDC (unweighted and after weighting in the base case and scenario 1) 63
Table 21. 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 1) 64
Table 22. List of studies excluded from mITT population sensitivity analyses 66
Table 23. Heterogeneity (I^2) in the mITT population network (overall period and 3+ months piecewise) 66
Table 24. Summary of any grade AEs in AEGEAN in the overall study period, safety analysis set 72
Table 25. Summary of most common AEs in AEGEAN (overall study period), safety analysis set[a] 73
Table 26. Summary of AEs possibly related to surgery and surgical complications in AEGEAN (post-surgery period), underwent surgery, modified safety analysis set 74
Table 27. Summary of AEs possibly related to treatment or surgery at D120SU 74
Table 28. Summary of discontinuations at D120SU 76
Table 29. Summary of NICE TAs 85
Table 30. Characteristics of de novo economic model 89
Table 31. Overview of the clinical inputs 94
Table 32. Goodness of fit statistics for AEGEAN neoadjuvant PDC; EFS (post-3 months) 100
Table 33. Event-free survival landmarks (Neoadjuvant PDC) 102
Table 34. Neoadjuvant PDC EFS Validation: Landmark comparison 103

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Table 35. Piecewise (post-3 months) HRs for perioperative durvalumab vs. neoadjuvant PDC across the different settings 105
Table 36. Event-free survival landmarks (Perioperative durvalumab – base case) 106
Table 37. Event-free survival landmarks (Perioperative durvalumab – alternative base case) 107
Table 38. Piecewise (post-3 months) EFS comparator efficacy (neoadjuvant nivolumab + PDC) 108
Table 39. Piecewise (post-3 months) EFS comparator efficacy (surgery alone and adjuvant PDC) 108
Table 40. Site of recurrence inputs for EF 111
Table 41. Hazard ratio for RT alone vs. CRT based on meta-analysis by Hung et al. 2019[42] 115
Table 42. Survival curve weights based on treatments received in LRR 116
Table 43. Goodness of fit statistics; BSC; LRR to Death (TP5b) 117
Table 44. Survival curve weights based on treatments received in LRR 118
Table 45. Overview of the DCO and extrapolations used in the NICE appraisals and AEGEAN for the pembrolizumab regimens 122
Table 46. PFS curve weights based on treatments received in DM 124
Table 47. OS curve weights based on treatments received in DM 125
Table 48. EQ-5D utility index (UK weights) 127
Table 49. Summary of health state utility values 128
Table 50. Alternative utility estimates used in the base case and scenario analysis 128
Table 51. AE disutility values 129
Table 52. Age-adjusted utility 130
Table 53. Overview of key cost components 130
Table 54. Distribution of PDC in the neoadjuvant setting across comparators 131
Table 55. Overview of the assumptions used to inform the TDT in the neoadjuvant setting 133
Table 56. Proportion of patients in the neoadjuvant nivolumab + PDC arm receiving adjuvant treatments 134
Table 57. PDC treatments received in the adjuvant setting 134
Table 58. Overview of the assumptions used to inform the TDT in the adjuvant setting 135
Table 59. Dosing regimen per cycle in EF health state 136
Table 60. AEGEAN Patient characteristics informing the dosing calculations 137
Table 61. Unit acquisition costs 138
Table 62. Radiotherapy cost inputs 139
Table 63. Surgery costs 140
Table 64. Distribution of patients LRR by treatment modality based on treatment at EF and IO restrictions 142
Table 65. Treatment shares for LRR treatment modalities before and after re-weighting 142
Table 66. Dosing regimen per cycle in LRR health state 143
Table 67. Unit acquisition costs for the components of the LRR treatment options 143
Table 68. Overview of treatment duration, costs and proportion of patients receiving LRR treatments from a treatment basket 144
Table 69. Distribution of patients in DM1 by treatment modality based on treatment in EF and IO restrictions 146
Table 70. Distribution of patients in DM2 by treatment modality based on treatment at EF and IO restrictions 147

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Table 71. Dosing regimen per cycle in DM1 health state 147
Table 72. Dosing regimen per cycle in DM2 health state 148
Table 73. Unit acquisition costs for the components of the DM health state treatment options 148
Table 74. Overview of treatment duration, costs and proportion of patients receiving DM1 treatments from a treatment basket 149
Table 75. Overview of treatment duration, costs in the DM2 health state 150
Table 76. Monitoring costs 150
Table 77. Healthcare resource use by health state 151
Table 78. Healthcare resource unit costs 151
Table 79. Total healthcare resource use per health state cycle 152
Table 80. Terminal care cost 152
Table 81. Treatment-emergent grade 3/4 adverse event frequencies 153
Table 82. Adverse event unit costs 153
Table 83. Summary of key variables applied in the economic model 154
Table 84. Summary of key assumptions used in the economic model 157
Table 85. Base-case deterministic results: Perioperative durvalumab versus neoadjuvant PDC 161
Table 86. Base-case deterministic results: Perioperative durvalumab versus neoadjuvant nivolumab + PDC 161
Table 87. Base-case deterministic results: Perioperative durvalumab versus surgery alone 161
Table 88. Base-case deterministic results: Perioperative durvalumab versus adjuvant PDC 161
Table 89. Net health benefit (deterministic base-case) 162
Table 90. Base-case probabilistic results: Perioperative durvalumab versus neoadjuvant PDC 164
Table 91. Base-case probabilistic results: Perioperative durvalumab versus neoadjuvant nivolumab + PDC 164
Table 92. Base-case probabilistic results: Perioperative durvalumab versus adjuvant PDC 164
Table 93. Net health benefit (probabilistic base-case) 164
Table 94. Scenario analyses overview 172
Table 95. Scenario analyses results perioperative durvalumab versus neoadjuvant PDC 173
Table 96. Scenario analyses results perioperative durvalumab versus neoadjuvant nivolumab + PDC 173
Table 97. Scenario analyses results perioperative durvalumab versus surgery alone . 174
Table 98. Scenario analyses results perioperative durvalumab versus adjuvant PDC . 175

List of figures

Figure 1. Current pathway of care for resectable NSCLC in the UK 21
Figure 2. Current pathway of care, including proposed place of perioperative durvalumab in resectable NSCLC 25
Figure 3. AEGEAN study design 32
Figure 4. Flow diagram for MTP and alpha recycling 45
Figure 5. KM plot of EFS, mITT population 49
Figure 6. pCR at final analysis, mITT population 50
Figure 7. KM plot of OS, mITT population 51

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Figure 8. KM plot of OS at D120SU 52
Figure 9. MPR at final analysis, mITT population 54
Figure 10. Pathological regression, mITT population 54
Figure 11. Subgroup analyses of EFS (BICR using RECIST 1.1), mITT population 58
Figure 12. Subgroup analysis of pCR, mITT population 59
Figure 13. Anchored PAIC diagram for AEGEAN versus CheckMate 816 61
Figure 14. Network diagram of mITT AEGEAN versus adjuvant PDC and surgery alone, base case 66
Figure 15. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (base case) 68
Figure 16. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 1) 68
Figure 17. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 2) 69
Figure 18. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 3) 69
Figure 19. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 4) 70
Figure 20. Economic model structure 93
Figure 21. NICE TSD DSU 14 survival model selection process algorithm[129] 97
Figure 22. Log-cumulative hazard and smoothed Schoenfeld residuals plot for piecewise 3+ month interval; EFS 99
Figure 23. Smoothed hazards plots for piecewise 3+ month interval; EFS 100
Figure 24. Model fits to neoadjuvant PDC; EFS 101
Figure 25. Long-term predictions; modelled EFS versus observed EFS from AEGEAN 102
Figure 26. Five-year predictions; modelled EFS versus observed EFS from AEGEAN (weighted from the MAIC against CheckMate-816) – base case 106
Figure 27. Five-year modelled EFS versus observed EFS from AEGEAN (unweighted from the NMA) – alternative base case 107
Figure 28. Diagram of EFS modelling 110
Figure 29. EF to Death (TP3) model fits, pooled 112
Figure 30. Treatment pathway in locally advanced NSCLC 113
Figure 31. Overview of modelling from LRR to DM (TP4) 115
Figure 32. Overview of modelling from LRR to death (TP5) 117
Figure 33. LRR to Death (TP5b); BSC, model fits 118
Figure 34. Model structure with nested partitioned approach for the DM state 120
Figure 35. Treatment pathway in first line mNSCLC 121
Figure 36. Time to treatment discontinuation of perioperative durvalumab (KM Plot) .. 132
Figure 37. Time to treatment discontinuation of neoadjuvant PDC (KM Plot) 133
Figure 38. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant PDC 165
Figure 39. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant nivolumab + PDC 165
Figure 40. Incremental cost effectiveness plane: perioperative durvalumab versus surgery alone 166
Figure 41. Incremental cost effectiveness plane: perioperative durvalumab versus adjuvant PDC 166
Figure 42. CEAC: perioperative durvalumab versus neoadjuvant PDC 167
Figure 43. CEAC: perioperative durvalumab versus neoadjuvant nivolumab + PDC ... 167

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Figure 44. CEAC: perioperative durvalumab versus surgery alone 168
Figure 45. CEAC: perioperative durvalumab versus adjuvant PDC 168
Figure 46. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant PDC 169
Figure 47. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant nivolumab + PDC 169
Figure 48. Tornado diagram from OWSA - perioperative durvalumab vs. surgery alone 170
Figure 49. Tornado diagram from OWSA - perioperative durvalumab vs. adjuvant PDC 170

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Abbreviations

AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
AUC	Area under the serum drug concentration-time curve
BICR	Blinded independent central review
CI	Confidence interval
CD80	Cluster of differentiation 80
CDF	Cancer Drugs Fund
COVID-19	Coronavirus disease 2019
CRT	Chemoradiotherapy
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DFS	Disease-free survival
DIC	Deviance information criteria
EBUS	Endobronchial ultrasound
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5-Dimension, 5-Level health state utility index
ESMO	European Society for Medical Oncology
FDA	United States Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
IASLC	International Association for the Study of Lung Cancer
IgG1κ	Immunoglobulin G1 kappa
ITT	Intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat

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MMRM	Mixed model for repeated measures
MPR	Major pathological response
MTP	Multiple testing procedure
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NR	Not reported
NSCLC	Non-small cell lung cancer
OS	Overall survival
ORR	Objective response rate
pCR	Pathological complete response
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand-1
PD-L1 TC ≥ 1%	Expression of PD-L1 on tumor membrane, at any intensity, in ≥ 1% of tumor cells
PDC	Platinum-doublet chemotherapy
PET	Positron emission tomography
PFS	Progression-free survival
PORT	Post-operative radiation therapy
PRO	Patient-reported outcome
PS	Performance status
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QLQ-C30	30-item Core Quality of Life Questionnaire
QLQ-CL13	13-item Lung Cancer Quality of Life Questionnaire
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RVT	Residual viable tumour
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoC	Standard of care
TC	Tumor cells
TNM	Tumor, node, metastasis
UICC	Union for International Cancer Control
VAS	Visual analogue scale

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B.1. Decision problem, description of the technology and clinical care pathway

- **The single technology appraisal evaluates the clinical- and cost-effectiveness of durvalumab (IMFINZI®) as a perioperative treatment for resectable non-small cell lung cancer (NSCLC)**
    - The anticipated UK marketing authorisation is: [redacted]
- **Lung cancer is the third most common cancer and is the leading cause of cancer-related deaths in the UK[1]**
- **NSCLC accounts for approximately 80% to 85% of all lung cancer cases, making it the most prevalent form of lung cancer in the UK[2]**
- **Surgery with curative intent remains the primary treatment for eligible patients with early-stage NSCLC;[3-7] despite surgery, a high proportion of patients (62% with stage II and 76% with stage III NSCLC) experience disease recurrence or do not survive beyond 5 years post-surgery[8]**
    - Disease recurrence can occur rapidly, and the highest risk occurs in the immediate years following surgery (peaking around 12 months post-surgery)[9,10]
    - Patients with resectable NSCLC who develop recurrent disease have poor long-term survival outcomes and suffer increased humanistic and psychosocial burden, as such there is a need for improved curative-intent treatment options in resectable NSCLC[8,10-15]
- **Systemic neoadjuvant or adjuvant treatment can benefit patients but do not fully meet treatment goals as they achieve moderate risk of recurrence reduction and limited improvements in absolute survival[4,16]**
- **Combining the benefits of neoadjuvant and adjuvant immuno-oncology therapy with a perioperative regimen could yield further improvements in long-term clinical outcomes by priming the patient's immune system in the neoadjuvant setting and preventing the growth and spread of micrometastases before and after surgery (when risk of recurrence is highest) [9,10,17-19]**
- **The current pathway of care for the treatment of resectable NSCLC in the UK does not include a perioperative treatment regimen[3]**

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- **Perioperative durvalumab is studied in the AEGEAN trial, the first phase 3 study to describe significant event-free survival (EFS) and pathological complete response (pCR) benefits for a perioperative immuno-oncology therapy plus neoadjuvant platinum-doublet chemotherapy (PDC) in patients with resectable NSCLC[20].** [redacted]
- **The results of AEGEAN suggest that perioperative durvalumab meets the substantial need for a treatment that lowers the risk of recurrence or death and therefore improves the possibility of successful long-term outcomes, including 'cure', for patients with resectable NSCLC in the UK**

B.1.1 *Decision problem*

The objective of this single technology appraisal is to evaluate the clinical- and cost-effectiveness of durvalumab (IMFINZI®) in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery for the treatment of adults with resectable non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

The relevant comparators considered within the economic analysis are neoadjuvant nivolumab plus chemotherapy, adjuvant chemotherapy, and surgery alone/active monitoring (see Section B.1.3.3).

Table 1 presents the decision problem addressed in this submission and outlines any deviations from the NICE final scope.

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Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with untreated resectable NSCLC which has no EGFR or ALK genetic alterations	Adults with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements.	This submission focuses on the population in line with the anticipated regulatory license and the regulatory trial: *adults with resectable (tumours ≥ 4 cm and/or node-positive) Stage IIA-IIIB [N2] NSCLC and no known EGFR mutations or ALK rearrangements.*
Intervention	Durvalumab with chemotherapy for neoadjuvant treatment then durvalumab monotherapy for adjuvant treatment	As per scope	NA
Comparator(s)	Established clinical management without durvalumab, which may include: • Neoadjuvant nivolumab with chemotherapy • Neoadjuvant CRT • Platinum-based chemotherapy • Active monitoring • Pembrolizumab (subject to NICE appraisal) For people whose tumours express PD-L1 with at least a 50% tumour proportion score • Atezolizumab after adjuvant cisplatin-based chemotherapy (subject to NICE appraisal)	Established clinical management without durvalumab, which include: • Neoadjuvant nivolumab with chemotherapy • Platinum-based chemotherapy • Active monitoring Of note, durvalumab is compared with adjuvant platinum-based chemotherapy. Although neoadjuvant chemotherapy is part of the control arm of the regulatory trial AEGEAN, only adjuvant chemotherapy is recommended as a treatment option for some people in UK clinical practice.[3] Clinical experts across the UK were consulted in an advisory board confirmed patients are not offered neoadjuvant chemotherapy.[22]	Surgery alone is assumed to represent active monitoring, as such active monitoring is referred to as surgery alone throughout the submission. UK clinical experts, consulted in an advisory board, have confirmed that neoadjuvant CRT is not offered to patients with resectable NSCLC in UK clinical practice.[22] Neoadjuvant CRT is therefore not considered a relevant comparator for perioperative durvalumab. Pembrolizumab for adjuvant treatment of resected NSCLC is subject to an ongoing NICE appraisal. Pembrolizumab is therefore not a relevant comparator to durvalumab for this appraisal.

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			Atezolizumab monotherapy is recommended for use within the CDF for adjuvant treatment after complete tumour resection in adult patients with stage IIB or IIIA or N2 only IIIB NSCLC and with PD-L1 expression on ≥50% of tumour cells and whose disease has not progressed on recently completed adjuvant platinum-based chemotherapy.[23] Atezolizumab is not considered a relevant comparator for adjuvant durvalumab monotherapy because, as per NICE guidelines, new cancer products under appraisal should not include treatments recommended for use in the CDF as comparators. Atezolizumab was also placed at a separate decision point in the final scope pathway for ID6234.[24]
Outcomes	The outcome measures to be considered include: • EFS • DFS • pCR • Response rates • OS • Adverse effects of treatment • Health-related quality of life	As per scope.	AEGEAN is an ongoing study and per the MTP, DFS and OS will be formally assessed at subsequent interim and final analyses
Subgroups to be considered	If the evidence allows subgroups will be considered based on: • Whether durvalumab is used before and after surgery • PD-L1 tumour proportion score	Whilst pre-specified subgroup data from AEGEAN are presented in this submission, including for PD-L1 expression and disease stage (Section B.2.7), the cost-effectiveness analysis is based on the full mITT.	In AEGEAN durvalumab is assessed in the perioperative setting. Participants in the trial were randomised to neoadjuvant durvalumab + PDC followed by adjuvant durvalumab monotherapy versus neoadjuvant placebo + PDC followed by

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	• Disease stage		adjuvant placebo. As such, results are presented for the mITT population and not separately for durvalumab used before and after surgery.

Abbreviations: ALK, anaplastic lymphoma kinase; CDF, Cancer Drugs Fund; CRT, chemoradiotherapy; DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor receptor; mITT, modified intent-to-treat; MTP, multiple testing procedure; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PDC, platinum-doublet chemotherapy; PD-L1, programmed cell death ligand-1

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B.1.2 *Description of the technology being evaluated*

The mechanism of action, marketing authorisation, dose, method of administration, and price of perioperative durvalumab are described in Table 2.

Table 2. Technology being evaluated

UK approved name and brand name	Durvalumab (IMFINZI®)
Mechanism of action	Durvalumab is a high-affinity, human, recombinant IgG1κ mAb that selectively binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 receptors. In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.
Marketing authorisation/CE mark status	Durvalumab for the treatment of resectable NSCLC in the perioperative setting is under review by the MHRA. The anticipated approval date for durvalumab in the perioperative setting is [redacted] Durvalumab for the treatment of resectable NSCLC in the perioperative setting is also under review by the EMA and the anticipated date for EU marketing authorisation is [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**It is anticipated durvalumab will be indicated for:[25]** [redacted] **This is in addition to the following current indications:[26]** • *Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy* • *Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer* • *Durvalumab in combination with gemcitabine and cisplatin is indicated for the first line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer*
Method of administration and dosage	For resectable NSCLC, durvalumab is administered as an intravenous infusion over 1 hour at a dose of 1,500 mg[a] in combination with platinum-based chemotherapy every 3 weeks for up to 4 cycles prior to

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	surgery, followed by 1,500 mg as monotherapy every 4 weeks for up to 12 cycles after surgery.[25] Durvalumab will be administered until the patient experiences disease progression , disease recurrence, exhibits unacceptable toxicity, or reaches a maximum of 12 cycles after surgery.[25]
Additional tests or investigations	No additional tests or investigations outside current practice are expected.
List price and average cost of a course of treatment	The list price for durvalumab is £592 for a 120mg vial and £2466 for a 500mg vial. At list price, the total cost is approximately £69,779 per patient, based on treatment duration from the AEGEAN trial and including administration costs.
Patient access scheme (if applicable)	[redacted]

Abbreviations: ALK, anaplastic lymphoma kinase; CD80, cluster of differentiation 80; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; IgG1κ, immunoglobulin G1 kappa; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1;

[a] Resectable NSCLC patients with a body weight of 30 kg or less must receive weight-based dosing of durvalumab at 20 mg/kg. In combination with platinum-based chemotherapy dose at 20 mg/kg every 3 weeks (21 days) prior to surgery, followed by monotherapy at 20 mg/kg every 4 weeks after surgery until weight increases to greater than 30 kg.

Sources: cited in table

B.1.3 *Health condition and position of the technology in the treatment pathway*

B.1.3.1 *Disease overview*

Lung cancer is the third most common cancer and the leading cause of cancer-related deaths in the UK.[1] Between 2017 to 2019, lung cancer accounted for 21% of all cancer-related deaths in the UK.[1] In England, the age-standardised survival rate at 5 years for all lung cancers is 19.7%, which is considerably lower than other common cancers such as prostate (88.0%) and breast (86.0%) cancers.[27,28]

There are approximately 34,000 new cases of lung cancer diagnosed in the UK annually, the main types being NSCLC or small-cell lung cancer.[2,29] Non-small cell lung cancer constitutes approximately 80% to 85% of lung cancer cases, making it the most prevalent form of lung cancer in the UK.[2]

Due to the internal location of the tumour, patients may initially remain asymptomatic.[30] Once symptoms appear, they commonly include dyspnoea, fatigue, cough, pain, haemoptysis, hoarseness, and weight loss.[30] The wide-ranging nature of symptoms means they are not always immediately recognised as lung cancer, delaying diagnosis.[30]

Lung cancer is diagnosed and staged using a variety of tests including chest X-rays, computerised tomography (CT), or positron-emission tomography CT (PET-CT). Lung

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cancer samples are commonly acquired for diagnosis using bronchoscopy, endobronchial ultrasound (EBUS), or a percutaneous procedure (guided by CT or ultrasound).[3] Testing for driver genetic mutations e.g., EGFR mutations, may occur at this stage to identify patients likely to respond to targeted therapies. There is variation throughout the UK in turnaround times for genomic testing.[31] Delays in genomic or biomarker testing increase the risk of disease progression and the patient not receiving optimal treatment while waiting for results.[31]

The staging of NSCLC at diagnosis adheres to the American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) criteria, characterizing it as stage IA/B, IIA/B, IIIA/B/C, or IVA/B based on primary tumour size and spread (T), lymph node involvement (N), and presence of distant metastases (M).[32] Approximately 30% of NSCLC patients receive a stage II-III diagnosis.[29,33] Of note, the 7th AJCC/UICC staging criteria were superseded by the 8th edition in 2017, which gives different categorisations related to tumour size, extent of nodal involvement, and metastases.[34,35]

Surgery remains the primary curative-intent treatment for eligible patients with resectable NSCLC. [3] However, a high proportion of patients with resectable NSCLC (62% with stage II and 76% with stage III) experience disease recurrence or death within 5 years post-surgery (see Section B.1.3.4).[8]

Clinical experts across the UK consider patients who remain disease-free 5 years after treatment with curative intent to have a very low risk of recurrence and be functionally cured.[22] Recurrence more than 5 years after surgery is rare; less than 3% of patients with NSCLC who undergo curative resection develop recurrence more than 5 years after surgery.[36] For patients with post-surgical recurrence, the potential for a cure reduces as NSCLC reaches an advanced stage.[3] Patients with locoregional recurrence may still be treated with curative intent, but for patients who experience distant recurrence or progress to distant metastasis, there are limited curative treatment options available.[37,38]

B.1.3.2 *Burden to patients and society*

Patients with NSCLC have poorer physical health and poorer health-related quality of life (HRQoL) compared to the general population.[39,40] Early-stage lung cancer patients frequently have one or more chronic comorbidities such as cardiometabolic or respiratory-related conditions, anxiety, or depression.[13,41,42] The presence of two or more comorbidities in addition to symptoms of their lung cancer disease (e.g. dyspnoea), is associated with impaired HRQoL in these patients.[40]

Surgical resection with curative intent is recommended for patients with stage II-III NSCLC with the aim of completely removing the tumour (see Section B.1.3.3.1).[3-7] Patients with resected, early-stage NSCLC have poorer HRQoL, both physically and mentally, compared with the general population.[40,43] Although the physical component of HRQoL fluctuates, patients generally experience a significant decline in functioning ($p=0.012$) and performance status ($p=0.001$) over time (measured using Instrumental Activities of Daily Living and Karnofsky Performance Scale over 52 weeks).[41] The impact of early-stage NSCLC on patients' mental health is also substantial, with approximately

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20% and 10% of patients reporting clinically significant symptoms of anxiety and depression, respectively.[40]

Despite curative-intent treatment, patients with NSCLC undergoing resection can experience persistent symptom burden that impacts daily life and adds to psychosocial burden.[44] Symptoms like pain, fatigue, dyspnoea, and cough are prevalent immediately after surgery; however, dyspnoea and fatigue have been shown to persist 2 to 3 years after surgery.[15,43] The fear of disease recurrence, impacting over 80% of patients, leads to anxiety and distress. Adjusting to new roles or routines due to physical limitations further amplifies their psychosocial burden. [44] The limited efficacy of current treatments leads to high rates of recurrence and HRQoL decreases with each recurrence and advancing disease stage.[8,15,45] Distant metastases are associated with high symptom burden, worsening function, and reduced survival.[46,47]

Caregivers of NSCLC patients experience a considerable burden associated with care, with psychological distress and overall QoL deteriorating over time.[48,49] As a result of the long-term consequences of NSCLC, caregivers also need to adapt to new roles and responsibilities within family life that can be emotionally burdensome.[44]

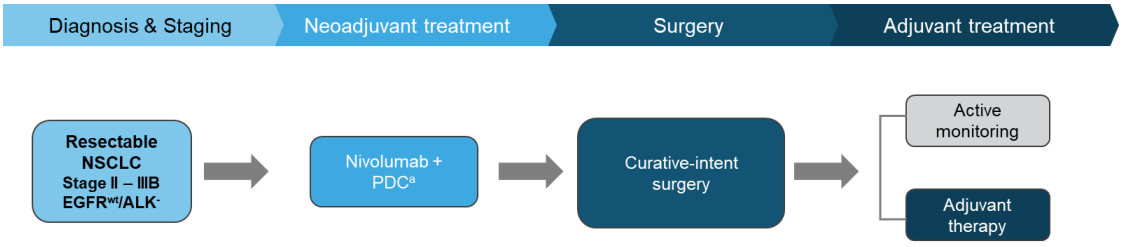
There is limited information describing the economic and societal burden of early-stage NSCLC in the UK; however, one study that collected data from 2009 to 2012 demonstrated a general trend of increased burden on the UK healthcare system for patients experiencing disease recurrence and distant metastases.[14] Patients with NSCLC who were of working age reported long-term absence from work, disability leave, and permanent disability.[14] The overall annual cost to society of early-stage, resected NSCLC (including direct, indirect, and out-of-pocket costs) was estimated at £267 million (cost year 2013).[14]

B.1.3.3 *Clinical pathway of care*

B.1.3.3.1 Current pathway of care for resectable NSCLC in the UK

The current pathway of care for patients with resectable NSCLC (without EFGR or ALK mutations) is shown in Figure 1.

Figure 1. Current pathway of care for resectable NSCLC in the UK



Abbreviations: ALK-, anaplastic lymphoma kinase negative; EGFR^{wt}, epidermal growth factor receptor wild-type; NSCLC, non-small cell lung cancer; PDC, platinum-doublet chemotherapy

[a] Stage IB-IIIA, resectable (tumours ≥4 cm or node positive) NSCLC

Sources: NICE 2023(NG122)[3]; NICE 2023(TA876)[50]

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Clinical guidelines for the management of NSCLC recommend surgical resection with curative intent for patients with operable tumours who are fit for surgery.[3-7] Risk of surgical mortality, lung and cardiovascular function determine a patient's suitability for resection.[3] The National Lung Cancer Audit (2022) reports that in 2019, approximately 50% of stage II patients underwent surgery, while the surgery rate for stage IIIA-B patients was 12%. These proportions decreased in 2020 to 41% and 8% for stage II and IIIA-B patients, respectively, likely influenced by the challenges posed by COVID-19.[51] It is estimated that approximately 1,860 patients in England and Wales have stage IIA-IIIB resectable, treatment-naive NSCLC.

Despite surgical removal of the tumour, recurrence rates following resection remain high for patients with resectable NSCLC.[8] Systemic therapy, either before surgery (neoadjuvant) or after surgery (adjuvant), may be provided, with the aim to reduce the risk of recurrence and increase long-term survival.[4,16] Neoadjuvant and adjuvant chemotherapy regimens offer modest benefits to patients compared with surgery alone. The 5-year absolute survival benefit of adjuvant chemotherapy varies with stage of disease from 3% for patients with stage IB disease to 5% for stage III disease.[16] Patients treated with neoadjuvant chemotherapy had a nonsignificant trend towards longer disease-free survival (DFS) than those undergoing surgery alone.[52]

Neoadjuvant chemotherapy is not recommended for patients with stage I-II NSCLC outside of a clinical trial.[3] The only neoadjuvant chemotherapy recommended in the UK is chemoradiotherapy (CRT) (chemotherapy in combination with radiotherapy) for patients with operable, stage IIIA-N2 NSCLC.[3] In either a neoadjuvant or adjuvant setting, CRT is only administered in around 5% of stage IIIA NSCLC patients in England.[53] This is supported by a survey of physicians in England which reports only 10% of physicians are using trimodality treatment regularly and 85% are using it either occasionally, rarely, or not at all.[54] In the advisory board, clinical experts unanimously confirmed that neoadjuvant chemotherapy or CRT is not offered to patients with resectable NSCLC in UK clinical practice.[22]

In the UK, adjuvant platinum-based chemotherapy is recommended for patients with a good performance status (World Health Organisation [WHO] 0 or 1) and T2b-4, N0, M0 NSCLC (i.e., tumour size between 4cm and 5cm and no nodal involvement or metastatic disease).[3,55] A large proportion of eligible patients either choose not to have chemotherapy or are not fit enough to tolerate it following surgery due to its toxicities and limited efficacy when used on its own (≤5% absolute survival benefit at 5 years).[16,52] A retrospective observational study reported 13%, 44%, and 50% of patients with completely resected stage IB, II, and IIIA NSCLC, respectively, had received adjuvant chemotherapy in the UK (N=293, patients diagnosed between January 2009 to December 2011).[37] When discussed in the 2024 advisory board, clinical experts stated only a small proportion of patients with resectable NSCLC receive adjuvant chemotherapy in UK clinical practice as most patients receive immuno-oncology therapy.[22] Of the patients that do receive adjuvant chemotherapy, carboplatin is the preferred platinum agent.[22]

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Immuno-oncology therapies are being evaluated for the treatment of resectable NSCLC in the neoadjuvant and adjuvant settings. Nivolumab plus chemotherapy was recommended by NICE in March 2023 as neoadjuvant treatment for patients with stage IB-IIIA resectable (tumours ≥4 cm or node positive) NSCLC.[50]

Immuno-oncology therapies used in the neoadjuvant setting prime the body's immune response to target primary tumour cell activity before surgery.[17,18] Immuno-oncology therapies may also act as a debulking agent, promote responses against micrometastases already present, and can promote the immune system's killing of tumour cells released during surgery, thereby limiting recurrence.[18,19] Importantly, the addition of neoadjuvant immuno-oncology therapies to neoadjuvant chemotherapy does not impact surgery in terms of the proportion of patients receiving surgery and delays to surgery.[56]

In September 2022, NICE recommended adjuvant atezolizumab for use within the Cancer Drugs Fund (CDF) for select patients with stage II-IIIA NSCLC whose tumours have PD-L1 expression ≥50% and have not progressed after platinum-based adjuvant chemotherapy.[23] Adjuvant atezolizumab was recommended as a treatment option after adjuvant chemotherapy as it has been shown to prolong DFS compared with best supportive care.[57] Since adjuvant atezolizumab is only available via the CDF, it is not considered routine clinical practice, and as per NICE guidelines, new cancer products under appraisal should not include treatments recommended for use in the CDF as comparators.[58] In addition, atezolizumab is placed after adjuvant chemotherapy, at a separate decision point to durvalumab in the treatment pathway.[24] Therefore, atezolizumab is not a relevant comparator in the adjuvant phase for perioperative durvalumab in this submission.

Osimertinib is another adjuvant treatment available via the CDF for patients with stage IB-IIIA NSCLC who have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations only. As AEGEAN excluded patients with EGFR mutations and ALK gene rearrangements, osimertinib is out of scope for this appraisal.[59]

B.1.3.3.2 Other relevant clinical guidelines

Guidelines for the management of lung cancer relevant to the UK include those published by the European Society for Medical Oncology (ESMO) and Scottish Intercollegiate Guideline Network (SIGN) Guideline 137.[4,5] In patients with completely resected, stage II-IIIA NSCLC, SIGN and ESMO recommend adjuvant platinum-based chemotherapy. An update to the ESMO guidelines in 2021 discussed early data for neoadjuvant nivolumab plus chemotherapy and adjuvant atezolizumab, but are yet to make recommendations on their use in routine clinical practice.[6]

B.1.3.4 *Unmet need for resectable NSCLC in the UK*

Disease recurrence in the form of local, locoregional, or distant metastases, progresses a patient's pathological stage from early to advanced stage NSCLC.[60] Curative intent treatment options are limited for patients with disease recurrence and survival outcomes worsen by stage.[3,60-62] In England, the 5-year survival rate for stage I lung cancer is 61%, whereas stage II, III, and IV are 39%, 15%, and 4%, respectively (note, the inclusion of

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patients ≥75 years of age may skew these rates downward).[27] Although the prognosis of early-stage NSCLC is better than advanced stage, survival outcomes for early-stage NSCLC still lag behind breast cancer in which 73.2% and 89.5% of patients diagnosed with stage II and III survive 5 years, respectively.[27]

A high proportion of patients with resectable NSCLC (62% with stage II and 76% with stage III) experience disease recurrence or death within 5 years post-surgery.[8] In a cohort of patients who had completely resected stage II-IIIB NSCLC and later experienced recurrence, the median time until recurrence after surgery, despite receiving adjuvant chemotherapy (with or without radiation), was 13.7 months.[11]

This indicates a rapid occurrence of disease recurrence, with the highest risk in the immediate years post-surgery (peaking around 12 months).[9] After the initial 12 months, the risk of recurrence typically reduces but persists for up to 5 years, with a small number of patients still experiencing recurrence even after 5 years.[9,10,36,63]

Disease recurrence after resection in patients with early-stage NSCLC reduces survival outcomes. Patients with early-stage NSCLC who experience disease recurrence have a 2.5 times higher risk of death ($p<0.001$).[10] Further, the 5-year survival rate following recurrence is low (<30%).[10,12]

Historically, the first recurrence involves distant metastases in the majority of cases, most commonly occurring in the brain and bone, thus prognosis and survival for these patients is particularly poor (5-year post-distant recurrence survival <10%).[9,12,63-65] For patients with NSCLC who experience recurrence following resection, the opportunities for further treatment with curative intent are limited and outcomes (prognosis, HRQoL) are generally poor (see Section B.1.3.2).[3,61,62] Therefore, treatment in the resectable setting represents the best chance for the patient to remain recurrence-free and achieve successful long-term survival outcomes.

Additional to surgery, systemic therapies given in the neoadjuvant setting or adjuvant setting can benefit patients by reducing recurrence and improving survival.[4,16,50] However, there are only two NICE recommended neoadjuvant options (nivolumab plus chemotherapy and CRT) and one adjuvant option (chemotherapy) for patients with resectable NSCLC. Until recently, there was no NICE recommended neoadjuvant treatment for the majority of early-stage NSCLC patients, only CRT for select patients with stage IIIA N2 disease.[3] Neoadjuvant nivolumab plus chemotherapy is now recommended by NICE (2023).[50]

There have been changes in the post-surgery setting with new treatment options for select patients now available; however, for the majority of patients adjuvant chemotherapy for eligible patients or surgery only with active monitoring remain the current standard of care (SoC).[3] Atezolizumab has been recommended by NICE for inclusion in the CDF but as a treatment option after adjuvant chemotherapy and it is not established in routine clinical practice in the UK.[23]

To date, immuno-oncology therapies used either in the neoadjuvant or adjuvant settings, have demonstrated reduced recurrence and improved survival benefits for patients with

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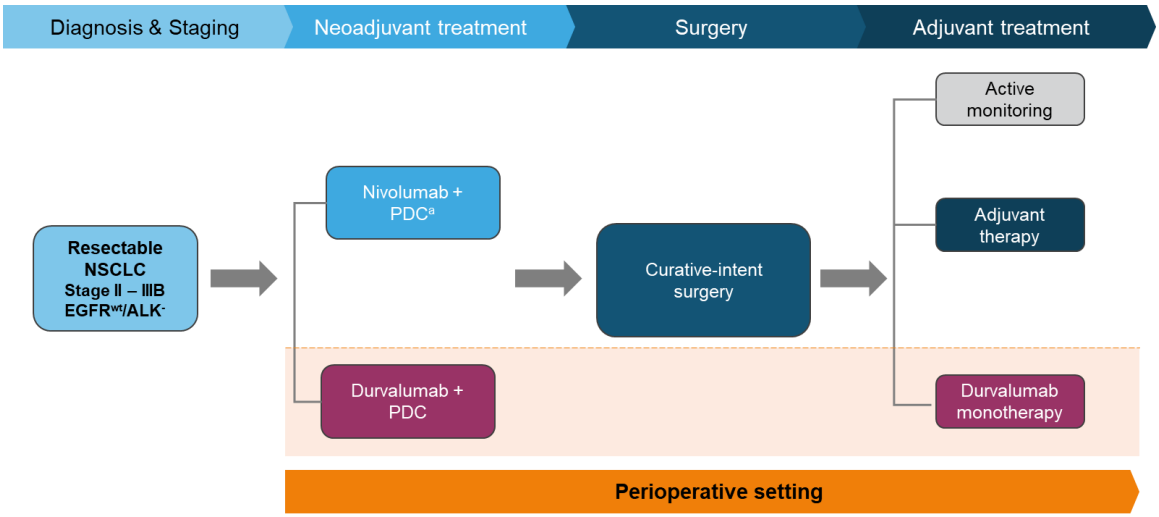
resectable NSCLC.[57,66,67] Immuno-oncology therapies in the neoadjuvant setting have also demonstrated improvements in pathological complete response (pCR) that are associated with improvements in event-free survival (EFS) and overall survival (OS) (See Section B.2.6.2).[66,68,69] A perioperative regimen, treating with the same immuno-oncology therapy before and after surgery, may prime the patient's immune system before surgery in the neoadjuvant setting and prevent the growth and spread of micrometastases in the neoadjuvant-, as well as the adjuvant setting when the risk of recurrence is the highest.[9,10,17-19] The adjuvant component of a perioperative regimen will provide continued immunosurveillance of micrometastatic disease and safeguard a good surgical outcome.[70,71] A perioperative immuno-oncology therapy regimen, of which there is currently none available to UK patients, has the potential to further improve long term outcomes for patients with resectable NSCLC and the healthcare system in the UK.

B.1.3.5 *Proposed place of perioperative durvalumab in the clinical care pathway for resectable NSCLC in the UK*

Figure 2 shows the proposed positioning of perioperative durvalumab in the current pathway of care for resectable NSCLC in the UK. It is expected that adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements will be eligible for treatment with perioperative durvalumab in UK clinical practice.[9,10,17-19,25]

The results of the AEGEAN study to date support the positioning of durvalumab as a perioperative treatment that addresses the substantial unmet need among patients who, despite undergoing curative-intent resection, still develop disease recurrence.[8] Moreover, the positioning of durvalumab as a perioperative treatment provides an opportunity to reduce the risk of recurrence or death and therefore improves the possibility of successful long-term outcomes, including 'cure', for patients with resectable NSCLC in the UK.

Figure 2. Current pathway of care, including proposed place of perioperative durvalumab in resectable NSCLC



Abbreviations: ALK-, anaplastic lymphoma kinase negative; CRT, chemoradiotherapy; EGFR^{wt}, epidermal growth factor receptor wild-type; NSCLC, non-small cell lung cancer; PDC, platinum-doublet chemotherapy

[a] Stage IB-IIIA, resectable (tumours ≥4 cm or node positive) NSCLC

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B.1.4 *Equality considerations*

No equality issues are anticipated.

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B.2. Clinical effectiveness

- **AEGEAN is a phase 3 double-blind, placebo-controlled, randomised, multicentre, international study examining the efficacy and safety of perioperative durvalumab + neoadjuvant platinum-doublet chemotherapy (PDC) versus perioperative placebo + neoadjuvant PDC for the treatment of patients with resectable stage IIA-IIIB[N2] (AJCC 8th edition) NSCLC**
- **AEGEAN has two primary endpoints, EFS and pCR. The use of EFS as a primary endpoint is aligned with the treatment goals of the resectable NSCLC setting as it considers the occurrence of multiple patient-relevant events (progression events precluding surgery, recurrence events after surgery, and death), provides a direct measure of treatment efficacy across both neoadjuvant and adjuvant treatment periods with surgery as a curative intent therapeutic strategy, and is not confounded by subsequent therapy following progression or recurrence**
- **Perioperative durvalumab + neoadjuvant PDC significantly improved EFS versus perioperative placebo + neoadjuvant PDC in patients with stage IIA-IIIB, resectable NSCLC without EGFR/ALK mutations, providing a 32% overall reduction in the risk of an EFS event :**
    - At the first interim analysis of EFS (data cut-off [DCO] 10 November 2022), median EFS in the perioperative durvalumab arm was not reached and was 25.9 months in the perioperative placebo arm (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.53 to 0.88; p=0.004)
    - An EFS benefit (HR < 1) was observed across all prespecified subgroups, including disease stage and PD-L1 expression, and regardless of the planned neoadjuvant platinum agent; HR was 0.59 (95% CI 0.35 to 1.00) for cisplatin and 0.73 (95% CI 0.54 to 0.98) for carboplatin
- **Treatment with perioperative durvalumab + neoadjuvant PDC resulted in a significant improvement in pCR compared with perioperative placebo + neoadjuvant PDC:**
    - At the primary analysis (DCO 14 January 2022), pCR was achieved in 17.9% of patients in the perioperative durvalumab arm compared with 4.9% of patients treated with perioperative placebo, resulting in a statistically significant treatment difference of 13.0% (95% CI 7.1 to 19.5; p<0.001)
    - The result for pCR at the final analysis (DCO 10 November 2022) was consistent with the pCR result at the primary analysis (DCO 14 January 2022) with a difference in proportions of 13.0% (95% CI 8.7 to 17.6) in favour of perioperative durvalumab
- **Overall survival (OS) is a secondary endpoint in AEGEAN where the day 120 safety update (D120SU) provided as part of US Food and Drug Administration (FDA)-specific regulatory procedures (DCO [redacted])**

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[redacted]
(HR [redacted] (95% CI [redacted] to [redacted]))[21]

- **Indirect treatment comparisons (ITCs) comparing EFS for perioperative durvalumab + neoadjuvant PDC versus neoadjuvant nivolumab + PDC, adjuvant PDC, or surgery alone were conducted and resulted in an EFS gain in favour of durvalumab + neoadjuvant PDC versus all comparators:**
    - For the matching-adjusted indirect comparison versus neoadjuvant nivolumab + PDC, the base case analysis resulted in a numerical benefit in EFS HR for perioperative durvalumab versus neoadjuvant nivolumab of [redacted] (95% CI [redacted] to [redacted])
    - For the network meta-analyses versus adjuvant PDC and surgery alone (mITT population), there was an estimated EFS benefit for perioperative durvalumab versus both comparators
- **AEGEAN is ongoing and will provide further evidence for longer-term EFS, as well as DFS and OS at future planned analyses**
- **Regardless of disease stage, the addition of perioperative durvalumab to neoadjuvant PDC did not adversely impact the feasibility or timing of surgery in patients with resectable NSCLC and resulted in numerically higher R0 resection rates**
- **Health-related quality of life (HRQoL) was assessed using EQ-5D-5L.** [redacted]
- **Perioperative durvalumab + neoadjuvant PDC was associated with a manageable safety profile that was consistent with the known safety profiles of durvalumab and chemotherapy:**
    - There was no increase in frequency or severity of adverse events (AEs)
    - Perioperative durvalumab treatment did not affect the proportion of patients with any grade AE possibly related to surgery, or with any surgical complication
- **Taken altogether, these results suggest that perioperative durvalumab meets the substantial need for a treatment that lowers the risk of recurrence or death and therefore improves the possibility of successful long-term outcomes, including 'cure', for patients with resectable NSCLC in the UK**

B.2.1 *Identification and selection of relevant studies*

A *de novo* systematic literature review (SLR) was conducted to identify evidence for the clinical efficacy and safety of perioperative durvalumab for the treatment of resectable, NSCLC.

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The SLR had a broad scope to identify all studies for relevant comparators defined by the NICE Final Scope for use in the indirect treatment comparison (ITC). Comparators include treatments for stage I–III NSCLC in patients who are candidates for or have undergone surgical resection. The inclusion of stage I accounts for differences in staging systems used between trials e.g., CheckMate 816[66] includes stage IB according to AJCC 7th edition and therefore would have been excluded if the SLR was limited to stage II-III.

Full details of the methods used to identify and select clinical evidence relevant to the Final Scope is provided in Appendix D. In summary, the SLR adhered to the guidelines published by the University of York Centre for Reviews and Dissemination (CRD) and the Cochrane Handbook for Systematic Reviews of Interventions. The SLR study question was specified using the PICOS framework (Population, Intervention, Comparator, Outcome, and Study type).

MEDLINE, Embase, The Cochrane library and the York CRD database were searched to identify relevant published literature for the clinical SLR. Key eligibility criteria for the SLR included patients with stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC undergoing any or no treatment prior to surgery for stage I–III NSCLC.

B.2.2 *List of relevant clinical effectiveness evidence*

The SLR identified a single randomised controlled trial (RCT), AEGEAN, evaluating perioperative durvalumab in the population of interest to this submission: patients with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements (Table 3). Data from AEGEAN has been included in the economic model presented in this submission. A detailed overview of AEGEAN is presented in Table 4.

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Table 3. List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Is study excluded from further discussion? If yes state rationale
AEGEAN	Adults (≥18 years with previously untreated resectable Stage IIA to select (N2) IIIB NSCLC (per AJCC Staging Manual, 8th edition)[72]	Durvalumab + platinum-based doublet chemotherapy[a] prior to surgery followed by durvalumab monotherapy post-surgery	Placebo + platinum-based doublet chemotherapy prior to surgery, followed by placebo alone post-surgery)	Heymach et al. *N Engl J Med*. Nov 2 2023;389(18):1672-1684[20] Heymach et al. *Clin Lung Cancer.* 2022;23(3):e247-e251[73] Heymach et al. *Oral Presentation AACR Annual Meeting, April 14-19, 2023*[74] AstraZeneca. AEGEAN Clinical Study Report. 2023[75]	No

Abbreviations: AJCC, American Joint Committee on Cancer; NSCLC, non-small cell lung cancer

[a] Platinum-based doublet chemotherapy includes carboplatin/paclitaxel, cisplatin/gemcitabine, pemetrexed/cisplatin, or pemetrexed/carboplatin

Sources: cited in table

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Table 4. Clinical effectiveness evidence

Study	AEGEAN: Heymach et al. 2023[20]
Study design	AEGEAN is an ongoing, phase 3, double-blind, placebo-controlled, randomised, multi-center, international study
Population	Adults (≥18 years) with previously untreated resectable stage IIA to select (N2) IIIB NSCLC (per AJCC Staging Manual, 8th edition)[72]
Intervention(s)	Durvalumab + platinum-based doublet chemotherapy[a] prior to surgery followed by durvalumab monotherapy post-surgery
Comparator(s)	Placebo + platinum-based doublet chemotherapy prior to surgery, followed by placebo alone post-surgery
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	Primary: • pCR • **EFS[b]** Secondary • MPR • DFS[c] • OS[d] • pCR, MPR, EFS, DFS, OS in PD-L1 TC ≥1% group • Surgical outcomes HRQoL/PRO • EORTC QLQ-C30, version 3 • EORTC QLQ-LC13 • EQ-5D-5L Safety
All other reported outcomes	Pharmacokinetics Immunogenicity

The primary analyses were conducted using the mITT population. The mITT includes all randomised patients excluding those with EGFR mutations or ALK gene rearrangements.

Abbreviations: ALK, anaplastic lymphoma kinase; DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-LC13, EORTC QLQ Lung Cancer Module; mITT, modified intent-to-treat; MPR, major pathological response; NA, not applicable; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PD-L1 TC ≥1%, expression of PD-L1 on tumour membrane, at any intensity, in ≥1% of tumour cells; RECIST, Response Evaluation Criteria in Solid Tumours

[a] Platinum-based doublet chemotherapy includes carboplatin/paclitaxel, cisplatin/gemcitabine, pemetrexed/cisplatin, or pemetrexed/carboplatin

[b] EFS is defined as the time from randomisation to progression of disease determined by blinded independent central review per RECIST v1.1, death due to any cause, disease progression that precludes surgery, or disease progression discovered while attempting surgery

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[c] DFS is defined as the time from resection until local or distant disease recurrence in the subpopulation of patients who were disease-free following resection, or death due to any cause, whichever occurs first

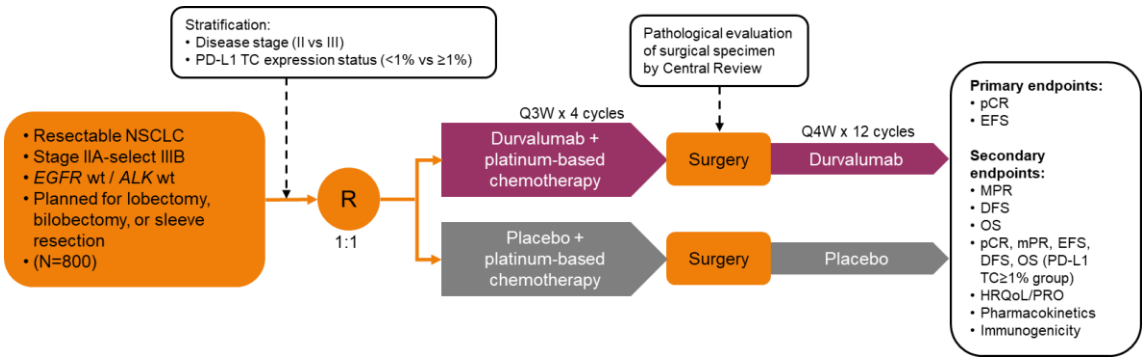
[d] OS is defined as the time from randomisation until death due to any cause

B.2.3 *AEGEAN*

B.2.3.1 *Summary of methods*

AEGEAN (NCT03800134) is an ongoing phase 3, double-blind, placebo-controlled, randomised, multicentre, international study to examine the efficacy and safety of neoadjuvant durvalumab + neoadjuvant PDC followed by adjuvant durvalumab monotherapy (hereafter referred to as perioperative durvalumab) versus neoadjuvant placebo + neoadjuvant PDC followed by adjuvant placebo (hereafter referred to as perioperative placebo) for the treatment of adult patients with resectable Stage IIA-IIIB [N2], AJCC 8th edition, NSCLC.[20] The trial design for AEGEAN is summarised in Figure 3.

Figure 3. AEGEAN study design



The primary analyses were conducted using the mITT population. The mITT includes all randomised patients excluding those with EGFR mutations or ALK gene rearrangements

Abbreviations: ALK, anaplastic lymphoma kinase; DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL, health-related quality of life; mITT, modified intent-to-treat; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; PD-L1 TC, programmed cell death ligand -1 tumour cells; PRO, patient-reported outcome; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomise

Sources: Heymach et al. 2023[20]

Table 5 below presents the full methods of AEGEAN, with inclusion and exclusion criteria described in Table 6.

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Table 5. Summary of AEGEAN methodology

Trial number (acronym)	**AEGEAN**
Settings and locations	231 sites in 28 countries across Europe, Asia-Pacific, North America, and South America. There were no UK sites in the trial.
Trial design	AEGEAN is an ongoing[a], phase 3, double-blind, placebo-controlled, randomised, multi-center, international study.
Eligibility criteria for participants	Eligible patients included adults (≥18 years) with resectable, histologically or cytologically documented, NSCLC (Stage IIA-IIIB [N2]; either squamous or non-squamous). Patients must have had no previous treatment for resectable NSCLC. Patients must have a World Health Organization (WHO)/ECOG PS of 0 or 1 at enrolment, confirmation of tumour PD-L1 status, and be evaluable for EGFR and ALK status.
Sample size	Based on a total of 0.5% alpha allocated to the pCR endpoint, a sample size of approximately 740 eligible patients was planned for the mITT population (randomised 1:1) to provide 55% power to detect a between-arm difference of 12% with a two-sided significance level of 0.008%. Based on a total of 4.5% alpha allocated to the EFS endpoint, for the first interim analysis of EFS and a true overall HR of 0.69, a study with 224 event-free survival events (per [BICR]) in the mITT population (N=740) would provide 50% power to demonstrate an EFS effect with a two-sided significance level of 0.665%. The actual number of randomised patients in the mITT population is 740 with: • n=366 in the perioperative durvalumab arm • n=374 in the perioperative placebo arm
Planned analysis	The mITT population was used for all efficacy and patient-reported outcome analyses. The type I error was controlled at a 5% 2-sided alpha level using a MTP. This was hierarchical starting with the two primary endpoints of pCR and EFS. The key secondary endpoint of MPR was also planned to be evaluated at the same times as pCR and tested according to an MTP to control the type I error rate. The overall 2-sided 5% type I error was split between pCR (0.5%) and EFS (4.5%) analyses. When statistical significance was demonstrated by pCR and MPR, EFS was tested with an alpha level of 5.0% with alpha recycling. DFS and OS were planned to be evaluated at the same times as EFS and tested according to the MTP.

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	Planned analyses included one interim and one final for pCR, and two interim and one final for EFS: • The first interim analysis of pCR was planned for when approximately 400 patients in the mITT population had a minimum of 7 months of follow-up (to allow time for surgery and pCR testing by central pathology laboratory) • The first interim analysis of EFS was planned for when approximately 224 EFS events had been reported (approximately 30% maturity in the mITT population)
Trial drugs	**Perioperative durvalumab arm (n=366)** Durvalumab 1500 mg IV in combination with platinum-based chemotherapy Q3W for maximum 4 cycles (neoadjuvant period) followed by durvalumab 1500 mg IV Q4W for maximum 12 cycles (post-surgery period). **Perioperative placebo arm (n=374)** Placebo IV (saline matching durvalumab volume) in combination with platinum-based chemotherapy Q3W for maximum 4 cycles (neoadjuvant period) followed by placebo IV Q4W for maximum 12 cycles (post-surgery period). The choice of chemotherapy regimen was determined by histology and at the investigator's discretion: • For non-squamous NSCLC: cisplatin plus pemetrexed or carboplatin plus pemetrexed • For squamous NSCLC: carboplatin plus paclitaxel or cisplatin plus gemcitabine (or carboplatin plus gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment)
Permitted and disallowed concomitant medication	**Permitted concomitant treatments** • Any medication or treatment deemed necessary by the investigators to provide adequate prophylactic or supportive care, excluding disallowed medications • Best supportive care included antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management • Post-operative radiation therapy (PORT) was allowed when indicated according to local guidance but PORT could not start until the first post-surgery RECIST 1.1 scan had been completed **Disallowed concomitant treatments** • Any investigational anticancer therapy other than those under investigation in this study • Monoclonal antibodies against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study

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	• Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study • Live attenuated vaccines • Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers • EGFR TKIs • Herbal anticancer remedies
Method of randomisation and blinding	Patients were randomised 1:1 to the study arms. Prior to randomisation, the investigator recorded the appropriate chemotherapy regimen for the patient in the Interactive Voice/Web Response System. Patients were then centrally randomised and investigator, patients, and study personnel remained blinded to study treatment. Randomisation was stratified by disease stage (stage II versus stage III) and by PD-L1 expression status (TC<1% versus TC≥1%).
Primary outcomes (including scoring methods and timings of assessments)	The AEGEAN study had two primary endpoints: • pCR: defined as the lack of any viable tumour cells after complete evaluation in the resected lung cancer specimen and all sampled regional lymph nodes and determined according to central pathological review using recommended methods and definitions described by IASLC in 2020 • EFS: defined as the time from randomization to progression of disease (determined by BICR per RECIST v1.1), death due to any cause, or progression of disease that precludes surgery or discovered while attempting surgery Tumour evaluation was conducted at baseline (prior to randomisation), after completion of neoadjuvant treatment (prior to surgery), post-surgery and prior to the first dose of adjuvant durvalumab/placebo, every 12 weeks for the first year post surgery, and every 24 to 48 weeks thereafter until RECIST 1.1-defined radiological progression of disease, consent withdrawal, or death.
Other outcomes	**Secondary** • MPR by central laboratory (per IASLC 2020) • DFS using BICR per RECIST 1.1 • OS • pCR, mPR, EFS, DFS, OS in PD-L1 TC ≥1% group

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	• Surgical outcomes **HRQoL/PRO (exploratory)** • EORTC QLQ-C30, version 3 • EORTC QLQ-LC13 • EQ-5D-5L **Safety** • AEs, physical examinations, vital signs (including BP, pulse, and ECGs), and laboratory findings (including clinical chemistry, haematology, and urinalysis)
Other outcomes used in the economic model/specified in the scope	The following outcomes are also used in the economic model: • Time to discontinuation of treatment • Site of recurrence
Pre-planned subgroups	AEGEAN EFS and pCR subgroup analyses included: • Age at randomisation (<65 years, ≥65 years) • PD-L1 expression status (<1%, 1-49%, ≥50%) • ECOG performance status (0, 1) • Race (Asian, Non-Asian) • Tumour histology (non-squamous, squamous) • Smoking status (current, former, never) • Disease stage, AJCC 8th edition (II, III) • Chemotherapy at baseline (cisplatin, carboplatin) • Lymph node station (N2 single station, N2 multi-station) • Geographic region (Asia, Europe, North America, South America)

Abbreviations: Abbreviations: ALK, anaplastic lymphoma kinase; AEs, adverse events; BICR, blinded independent central review; BP, blood pressure; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DFS, disease-free survival; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EGFR, epidermal growth factor; EGFR TKI, EGFR tyrosine kinase inhibitor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HR, hazard ratio; HRQoL, health-related quality of life; IASLC, International Association for the Study of Lung Cancer; MPR, major pathological response; MTP, multiple testing procedure; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PORT, post-operative radiation therapy; Q3W, every 3 weeks; Q4W, every 4 weeks; RECIST, Response Evaluation in Solid Tumours; TC, tumour cells

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[a] AEGEAN is an ongoing study and per the MTP, DFS and OS will be formally assessed at subsequent interim and final analyses. EFS efficacy data continues to be collected, AstraZeneca remains blinded to DFS, and the study continues in a blinded manner with patients and investigators blinded to treatment assignment

Sources: AstraZeneca 2023[75]; Heymach et al 2022[73]; Heymach et al. 2023[74]; Travis et al. 2020[76]; US NLM 2023[77]

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Table 6. Key eligibility criteria for AEGEAN

Inclusion criteria
• Male or female, age ≥18 years • Newly diagnosed and previously untreated patients with histologically or cytologically documented NSCLC with resectable (stage IIA to select [ie, N2] stage IIIB) disease • A WHO/ECOG PS of 0 or 1 at enrolment • At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 Target Lesion at baseline • No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines • Adequate organ and marrow function • Confirmation of a patient's tumour PD-L1 status • Provision of sufficient tumour biopsy sample for evaluation and confirmation of EGFR and ALK status • Planned surgery must comprise lobectomy, sleeve resection, or bilobectomy as determined by the attending surgeon • Adequate cardiac and lung function • Life expectancy of at least 12 weeks
Exclusion criteria
• History of allogeneic organ transplantation • Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome) • History of another primary malignancy • History of active primary immunodeficiency • Uncontrolled intercurrent illness • Active infection including tuberculosis hepatitis B and C, or human immunodeficiency virus • Deemed unresectable NSCLC by multidisciplinary evaluation • Patients who have pre-operative radiotherapy treatment as part of their care plan • Patients who have brain metastases or spinal cord compression • Stage IIIB N3 and Stages IIIC, IVA, and IVB NSCLC • Mean QTcF ≥ 470 ms calculated from up to 3 ECGs (within 30 minutes) • Known allergy or hypersensitivity to any of the study drugs or excipients • Existence of more than one primary tumour such as mixed small cell and NSCLC histology • Patients whose planned surgery at enrollment includes any of the following procedures: pneumonectomy, segmentectomies, or wedge resections • Any medical contraindication to treatment with platinum-based doublet chemotherapy as listed in the local labelling • Patients with a documented test result confirming the presence of EGFR mutation or ALK translocation

Abbreviations: ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PD-L2, programmed cell death ligand-2; RECIST, Response Evaluation in Solid Tumours; WHO, World Health Organisation
Sources:

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B.2.3.2 *Patient disposition*

Patients were randomised between January 2, 2019, and April 19, 2022. At the first interim analysis of EFS (DCO 10 November 2022), 1480 patients were enrolled, with 802 patients eligible to be randomised into the intent-to-treat (ITT) population. Of these, 740 patients were included in the primary efficacy population (mITT cohort), with 366 in the perioperative durvalumab arm and 374 patients in the perioperative placebo arm. At the first interim analysis of EFS in the mITT population, which was planned for 30% maturity of EFS events, the proportions of patients receiving neoadjuvant therapy, surgery, and adjuvant therapy were similar for both study arms (Table 7). At the first interim analysis of EFS, around [redacted]% of patients in both treatment arms remained on adjuvant treatment. A further interim analysis and one final analysis are planned for EFS as data collection continues.

Table 7. Patient disposition in AEGEAN at EFS first interim analysis, mITT population

Study phase	Perioperative durvalumab (n=366)	Perioperative placebo (n=374)
Neoadjuvant, n (%)		
Randomised	366 (100)	374 (100)
Received treatment	366 (100)	371 (99.2)
Completed 4 cycles of both chemotherapy agents	310 (84.7)	326 (87.2)
Completed 4 cycles of durvalumab/placebo	318 (86.9)	331 (88.5)
Surgery, n (%)		
Underwent surgery[a]	295 (80.6)	302 (80.7)
Completed surgery[a]	284 (77.6)	287 (76.7)
Received post-operative radiation therapy	26 (7.1)	21 (5.6)
Adjuvant (ongoing), n (%)		
Started durvalumab/placebo[a]	241 (65.8)	237 (63.4)
Completed durvalumab/placebo	88 (24.0)	79 (21.1)
Discontinued durvalumab/placebo	68 (18.6)	70 (18.7)
Ongoing durvalumab/placebo	[redacted]	[redacted]

DCO 10 November 2022

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

[a] For patients to be eligible for adjuvant durvalumab or placebo, surgery must have been completed with R0/R1 margins and no evidence of disease on post-surgical RECIST assessment

Sources: AstraZeneca 2023[75]; Heymach et al. 2023[20]

The first planned interim analysis of pCR (DCO 14 January 2022) was based on 402 patients who were randomised at least 7 months prior to DCO in order to allow time for surgery to take place and for completion of the pCR assessment by a central pathology laboratory. At the interim analysis of pCR, 196 patients were randomised to the perioperative durvalumab arm and 206 patients to the perioperative placebo arm. The proportion of patients who received neoadjuvant therapy and surgery were similar across the treatment arms (Table 8).

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Table 8. Patient disposition in AEGEAN at pCR first interim analysis, mITT population

Study phase	Perioperative durvalumab (n=196)	Perioperative placebo (n=206)
Neoadjuvant, n (%)		
Received treatment	[redacted]	[redacted]
Completed 4 cycles of both chemotherapy agents	[redacted]	[redacted]
Completed 4 cycles of durvalumab/placebo	[redacted]	[redacted]
Surgery, n (%)		
Underwent surgery[a]	[redacted]	[redacted]
Completed surgery[a]	[redacted]	[redacted]

DCO 14 January 2022

Abbreviation: DCO, data cut-off

[a] As per investigator assessment. Patients who 'underwent' surgery were those for whom curative-intent thoracic surgery was attempted regardless of whether it was completed. Patients who 'completed' surgery were those for whom curative-intent thoracic surgery was completed (assessed at the time of surgery).

Sources: AstraZeneca 2023[75]

As part of the US Food and Drug Administration (FDA)-specific regulatory procedures, a safety update was provided during review ("day 120 safety update" [D120SU] (DCO [redacted]). An OS update was also provided to the FDA at the same time point. Results from this update are presented in sections B.2.6.3.1 and B.2.10.2 of this submission.

[redacted]

At the D120SU (DCO [redacted]), [redacted]% of patients in the perioperative durvalumab arm and [redacted]% in the perioperative placebo arm had completed adjuvant durvalumab or placebo (Table 9).[21] [redacted] ([redacted]%) were continuing on study treatment (i.e., adjuvant durvalumab or placebo; compared with [redacted] patients ([redacted]%) at the primary analysis of EFS [DCO 10 November 2022]).[21]

Table 9. Patient disposition at D120SU

Study Phase	Perioperative durvalumab (N=366)	Perioperative placebo (N=374)
Screening		
Randomised, n (%)	366 (100)	374 (100)
Neoadjuvant Phase		
Received treatment, n (%)	[redacted]	[redacted]
Completed 4 cycles of both PDC agents, n (%)	[redacted]	[redacted]
Completed 4 cycles of durvalumab or placebo, n (%)	[redacted]	[redacted]

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Surgery		
Underwent surgery, n (%)	[redacted]	[redacted]
Did not undergo surgery, n (%)	[redacted]	[redacted]
Completed surgery, n (%)	[redacted]	[redacted]
Did not complete surgery†, n (%)	[redacted]	[redacted]
Received PORT n (%)	[redacted]	[redacted]
Adjuvant Phase (Ongoing)		
Started durvalumab or placebo, n (%)	[redacted]	[redacted]
Completed durvalumab or placebo, n (%)	[redacted]	[redacted]
Discontinued durvalumab or placebo, n (%)	[redacted]	[redacted]
Ongoing durvalumab or placebo, n (%)	[redacted]	[redacted]

DCO [redacted]

Note: A total of [redacted] patients in the ITT (all randomised patients) were ongoing adjuvant durvalumab/placebo at DCO [redacted] ([redacted])

Abbreviations: D120SU, day 120 safety update; DCO, data cut-off ; PDC, platinum-doublet chemotherapy; PORT, post-operative radiotherapy

Source: AstraZeneca 2024[21]

The median overall number of cycles of durvalumab and placebo received was [redacted] and [redacted] respectively ([redacted]% versus [redacted]% of patients completed all 16 planned cycles (Table 10).[21] In patients who received adjuvant treatment, the median number of cycles of durvalumab and placebo received was [redacted] in both arms ([redacted]% versus [redacted]% completed all 12 planned adjuvant cycles, respectively).[21]

Table 10. Number of cycles and completion of planned treatment at D120SU

	Perioperative durvalumab (N=401; [redacted] received adjuvant)	**Perioperative placebo (N=398; [redacted] received adjuvant)**
Number of Cycles		
Overall, median (Q1-Q3)	[redacted]	[redacted]
Adjuvant (for those received adjuvant), median (Q1-Q3)	[redacted]	[redacted]
Completion of planned treatment		
Overall, completed 16 cycles, n (%)	[redacted]	[redacted]
Adjuvant (for those received adjuvant), completed 12 cycles, n (%)	[redacted]	[redacted]

DCO [redacted]

Abbreviations: Q, quarter

Source: AstraZeneca 2024[21]

B.2.3.3 *Patient baseline characteristics*

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The patient and disease characteristics of patients in AEGEAN are presented for the mITT population at the primary analysis of EFS (N=740) in Table 11 and Table 12. Both patient (Table 11) and disease (Table 12) characteristics were generally well balanced across the two treatment arms. The only minor imbalance observed between the treatment arms was for sex (male: 68.9% and 74.3% respectively).

Table 11. Key patient demographics and baseline characteristics in AEGEAN

Characteristic	Perioperative durvalumab n=366	Perioperative placebo n=374
Median age, years (range)	65 (30–88)	65 (39–85)
≥75 years, n (%)	44 (12.0)	36 (9.6)
Male gender, n (%)	252 (68.9)	278 (74.3)
Race, n (%)		
Asian	143 (39.1)	164 (43.9)
White	206 (56.3)	191 (51.1)
Other	17 (4.6)	19 (5.1)
Region, n (%)		
Asia	142 (38.8)	163 (43.6)
Europe	141 (38.5)	140 (37.4)
North America	43 (11.7)	43 (11.5)
South America	40 (10.9)	28 (7.5)
Smoking status, n (%)		
Never	51 (13.9)	56 (15.0)
Former	220 (60.1)	223 (59.6)
Current	95 (26.0)	95 (25.4)

Sources: Heymach et al. 2023[20]

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Table 12. Key disease characteristics in AEGEAN

Characteristic	Perioperative durvalumab n=366	Perioperative placebo n=374
ECOG performance status, n (%)		
0	251 (68.6)	255 (68.2)
1	115 (31.4)	119 (31.8)
AJCC stage[a] at diagnosis, n (%)		
II	104 (28.4)	110 (29.4)
IIIA	173 (47.3)	165 (44.1)
IIIB	88 (24.0)	98 (26.2)
Histology type, n (%)		
Squamous	169 (46.2)	191 (51.1)
Non-squamous	196 (53.6)	179 (47.9)
TNM classification		
Primary tumour, n (%)		
T1	44 (12.0)	43 (11.5)
T2	97 (26.5)	108 (28.9)
T3	128 (35.0)	129 (34.5)
T4	97 (26.5)	94 (25.1)
Regional lymph nodes, n (%)		
N0	110 (30.1)	102 (27.3)
N1	75 (20.5)	87 (23.3)
N2	181 (49.5)	185 (49.5)
PD-L1 expression, n (%)		
TC <1%	122 (33.3)	125 (33.4)
TC 1-49%	135 (36.9)	142 (38.0)
TC ≥50%	109 (29.8)	107 (28.6)
Planned neoadjuvant platinum agent, n (%)		
Cisplatin	100 (27.3)	96 (25.7)
Carboplatin	266 (72.7)	278 (74.3)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand-1; TNM, tumour-node-metastasis

[a] AJCC 8th edition[72]

Sources: Heymach et al. 2023[20]

B.2.4 *Statistical analysis and definition of study groups*

B.2.4.1 *Definition of study groups*

Analysis sets in the AEGEAN study included the ITT, mITT, pCR interim analysis cohort, and safety analysis set, defined below in Table 13.

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Table 13. Study group definitions in AEGEAN

Population	Definition
ITT	All randomised patients
mITT[a]	ITT excluding patients with documented EGFR/ALK aberrations
pCR IA cohort	First ~400 patients in the mITT
Safety analysis set	ITT patients who received ≥1 dose of study treatment

[a] Patients with EGFR/ALK gene arrangements were analysed in a separate study[78]

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor; IA, interim analysis; ITT, intention to treat; mITT, modified intention to treat; pCR, pathological complete response
Sources: Heymach et al. 2023[20]

B.2.4.2 *Statistical analysis*

B.2.4.2.1 Hypothesis objective

The objective of AEGEAN was to demonstrate superiority of the perioperative durvalumab arm versus the perioperative placebo arm in terms of EFS and pCR in patients with resectable NSCLC and no EGFR mutations or ALK rearrangements (i.e. in the mITT population).

The hypothesis would be confirmed by testing for significant differences between the two treatment arms (H0: no difference between the perioperative durvalumab arm and perioperative placebo arm; H1: difference between the perioperative durvalumab arm and perioperative placebo arm) for each outcome in the mITT. The study was considered to have a positive outcome if either of the two endpoints, EFS or pCR in the mITT, showed a significant improvement in the perioperative durvalumab arm compared to the perioperative placebo arm.[20]

B.2.4.2.2 Analysis populations

AEGEAN planned for 800 eligible patients to be randomised in the ITT population, including 740 patients in the mITT population (after exclusion of patients with documented EGFR or ALK aberrations) (analysed in a separate study)[78]. Efficacy analyses were performed in the mITT population, and safety was assessed in all randomised patients who had received at least one dose of any trial treatment i.e., durvalumab, PDC, or placebo (the safety analysis set).[20]

B.2.4.2.3 Statistical and analytical methods

To assess any potential early indication of efficacy, interim analyses of pCR were performed after: 1) approximately 400 patients in the mITT population had approximately 7 months follow-up, allowing for surgeries, where applicable, and have complete central pathology assessment for pCR (inclusive of patients not eligible for surgery); and 2) approximately 800 patients had been randomised to the ITT population.[20] The final analysis of pCR was performed when all patients in the ITT population had the opportunity to undergo surgery (i.e., ~7 months follow-up) and complete central pathology assessment. The first interim analysis of EFS was performed at approximately 30% maturity for this endpoint (~224

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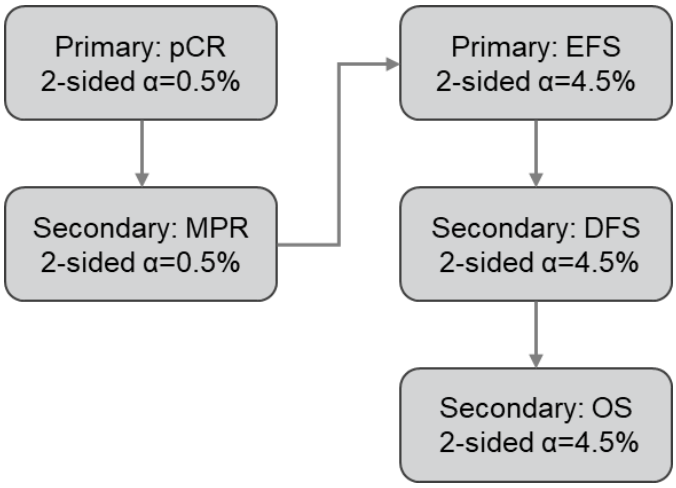
events) in the mITT population and coincided with the final analysis of pCR (DCO 10 November 2022).[20]

To strongly control the type I error at 5% (two-sided), a hierarchical MTP with gatekeeping strategy was used across the primary endpoints and alpha-controlled secondary endpoints (Figure 4). Hypotheses were tested using an alpha-exhaustive recycling strategy.[79] Initially, 0.5% alpha and 4.5% alpha were allocated to pCR and EFS, respectively. The alpha was split between the interim and final analyses using the Lan-DeMets spending function that approximates an O'Brien Fleming approach to account for multiple time point assessments.[20] Positivity for pCR enabled alpha recycling to the key secondary endpoint MPR, which in turn could be recycled to EFS (to provide a total 5% alpha).[20]

Figure 4. Flow diagram for MTP and alpha recycling



Note: The testing procedure is hierarchical, starting with testing the 2 primary endpoints pCR and EFS. The overall 2-sided 5% type I error is split between the 2 primary endpoints pCR and EFS. An alpha level of 0.5% is allocated to the pCR analysis and an alpha level of 4.5% is allocated to the EFS analysis. The study is considered to have a positive outcome if either of these 2 primary endpoints are statistically significant at any timepoint.

Per the planned MTP, if pCR is declared statistically significant, the 0.5% alpha will be recycled to MPR. If both pCR and MPR are declared statistically significant, the 0.5% alpha will be recycled to EFS, such that a total alpha level of 5% will be allocated to the EFS analyses. If EFS is declared statistically significant, then the alpha level utilized for the EFS analysis (either 4.5% alpha or 5% alpha) will be recycled to DFS, and if DFS is declared statistically significant, then the alpha level utilized (either 4.5% alpha or 5% alpha) will be recycled again to OS.

Abbreviations: DFS, disease-free survival; EFS, event-free survival; MPR, major pathological response; MTO, multiple testing procedure; OS, overall survival; pCR, pathological complete response

Source: Heymach et al. 2023[20]

B.2.4.2.4 Sample size and power calculation

Based on a total of 0.5% alpha allocated to the pCR endpoint, the planned interim analysis of pCR (assuming 400 patients in the mITT population at the interim analysis, 740 patients in the mITT population at the final analysis) had 55% power to detect a between-arm difference of 12% with a two-sided significance level of 0.008%.[20] Major pathologic response (an alpha-controlled secondary endpoint) was also formally analysed at the interim analysis. The statistical significance of pCR and MPR were not tested for at the final analysis if significance was demonstrated at the interim analysis.[20]

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For EFS, a 33-month nonlinear (k=2) accrual was assumed with a 3-month delay in hazard, whereby the assumed hazard ratio (HR) for the first 3 months was 1.0 and a HR of 0.63 was assumed after 3 months to give an approximate overall HR of 0.67 at the time of the final analysis.[20] Based on a total of 4.5% alpha allocated to the EFS endpoint for the first interim analysis of EFS and a true overall HR of 0.69, a study with 224 EFS events (per BICR) in the mITT population (N=740) would provide 50% power to demonstrate an EFS effect with a two-sided significance level of 0.665%.[20]

B.2.4.2.5 General analysis methodology

For pathological endpoints, response rates were compared between treatment arms using a stratified Cochran-Mantel-Haenszel test. The treatment effect was estimated by the differences in response rates, with their corresponding 95% confidence intervals (CIs) calculated by the stratified Miettinen and Nurminen method.[20] Event-free survival was compared between the treatment arms using a stratified log-rank test, with the treatment effect estimated by HRs and 95% CIs calculated with stratified Cox-proportional-hazards models. Medians and landmark rates for EFS were estimated using the Kaplan-Meier (KM) method.[20]

Subgroup analyses

Stratification for the primary and key secondary endpoints was by disease stage and PD-L1 expression. Planned analyses of the primary endpoints in predefined baseline subgroups were performed.[20] For pCR, the differences in response rates were calculated for each subgroup, with corresponding 95% CIs estimated using an unstratified Miettinen and Nurminen method. For EFS, hazard ratios and 95% CIs were calculated for each subgroup using a Cox-proportional-hazards model with treatment as the only covariate.[20]

B.2.5 *Critical appraisal of AEGEAN*

The quality assessment for the AEGEAN study is presented in Table 14. A quality assessment of all trials identified in the clinical systematic review can be found in Appendix D.

Table 14. Quality assessment results for AEGEAN

	Grade (yes/no/unclear)	Details
Was the randomisation method adequate?	Yes	Block randomisation stratified by disease stage (stage II vs III) and PD-L1 expression (<1% vs >=1%).
Was the concealment of treatment allocation adequate?	Yes	Assigned via interactive voice/web recognition system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics were similar between both treatment arms, but no formal analysis was reported.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	AEGEAN is a double-blind trial; the primary endpoint of EFS was assessed in a blinded fashion by independent central review.

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	Grade (yes/no/unclear)	Details
Were there any unexpected imbalances in drop-outs between groups?	No	There were no imbalances or unexpected drop outs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were reported for data which were available.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	AEGEAN included an ITT analysis; however, the mITT population was used for the primary efficacy analysis. Patients were removed as they were not eligible according to a protocol amendment.

Abbreviations: EFS, event-free survival; ITT, intent-to-treat; mITT, modified ITT; PD-L1, programmed cell death ligand-1

Source: Heymach et al. 2023[20]

B.2.6 *Clinical effectiveness results*

The results presented in this section are for the mITT population based on the DCO of 14 January 2022 for the primary analysis of pCR; and the DCO of 10 November 2022 for the primary analysis of EFS and final analysis of pCR.

As per the MTP, DFS was formally tested at the primary analysis of EFS (DCO 10 November 2022) but did not meet the prespecified boundary to declare statistically significance; OS was not therefore formally tested but descriptive summary of OS at first interim analysis of EFS (overall maturity: 22.1%) are provided in this report. The study team remain blinded to DFS, which will be tested when EFS data is at approximately 40% maturity (second interim analysis).[20]

B.2.6.1 *Primary outcome: EFS*

Surgery with neoadjuvant and/or adjuvant therapy is given with curative intent, with the aim to completely remove the primary tumour and reduce the risk of any subsequent recurrence. Progression precluding surgery or recurrence after surgery are both highly relevant events for patients, given the impact of progression/recurrence on subsequent prognosis and HRQoL.[10,12,15,45]

In AEGEAN, EFS is defined as the time from randomisation to an event of disease progression that precludes surgery, local or distant recurrence, or death due to any cause.[20] This means, EFS considers the occurrence of multiple patient-relevant events, provides a direct measure of treatment efficacy across both neoadjuvant and adjuvant treatment periods with surgery as a curative intent therapeutic strategy, and is not confounded by subsequent therapy following progression or recurrence. Since EFS includes progression events precluding surgery, recurrence events after surgery, and death, it is aligned with the treatment goals of this setting and measures the success/failure of neoadjuvant followed by adjuvant therapy.

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In addition to the intrinsic value of EFS as an endpoint in this setting, EFS is also a surrogate for OS. An SLR and meta-analysis conducted to explore the association between EFS and OS following neoadjuvant therapy for resectable Stage I–III NSCLC (excluding studies where the entire population had EGFR mutations), revealed a positive linear correlation and strong association between the two endpoints based on eight RCTs that reported HRs for both outcomes (weighted Pearson's coefficient, r=0.864; 95% CI 0.809 to 0.992; p=0.006; random effects meta-regression, R2=0.777).[80] Other studies have also shown the impact of recurrence on subsequent OS, when compared to patients who remain recurrence-free, following treatment in the neoadjuvant or adjuvant setting.[81,82]

At the primary analysis of EFS (DCO 10 November 2022 [N=740]), the median EFS follow-up in censored patients was 11.7 months (range 0.0 to 46.1) with a 31.9% maturity for mITT patients.[20] Treatment with perioperative durvalumab resulted in a statistically significant, clinically meaningful, and sustained improvement in EFS (using BICR per RECIST 1.1) compared with perioperative placebo.[75]

Median EFS for the perioperative durvalumab arm was not reached (NR) (31.9 months to NR) and was 25.9 months (18.9 months to NR) in the perioperative placebo arm resulting in a HR of 0.68 (95% CI 0.53 to 0.88; p=0.004) (Figure 5).[20,75] There was a 32% overall reduction in the risk of an EFS event (using BICR per RECIST 1.1) for patients in the perioperative durvalumab arm versus those in the perioperative placebo arm.[75]

The KM plot in Figure 5 below shows the curves for both treatment arms are similar until 3 months, then shows a clear and sustained separation in favour of the perioperative durvalumab arm. The curve separation after 3 months corresponds to the planned timing of the first RECIST scan after randomisation (i.e., following completion of neoadjuvant therapy and prior to surgery). The prespecified sensitivity analyses were consistent with the primary analysis.[75]

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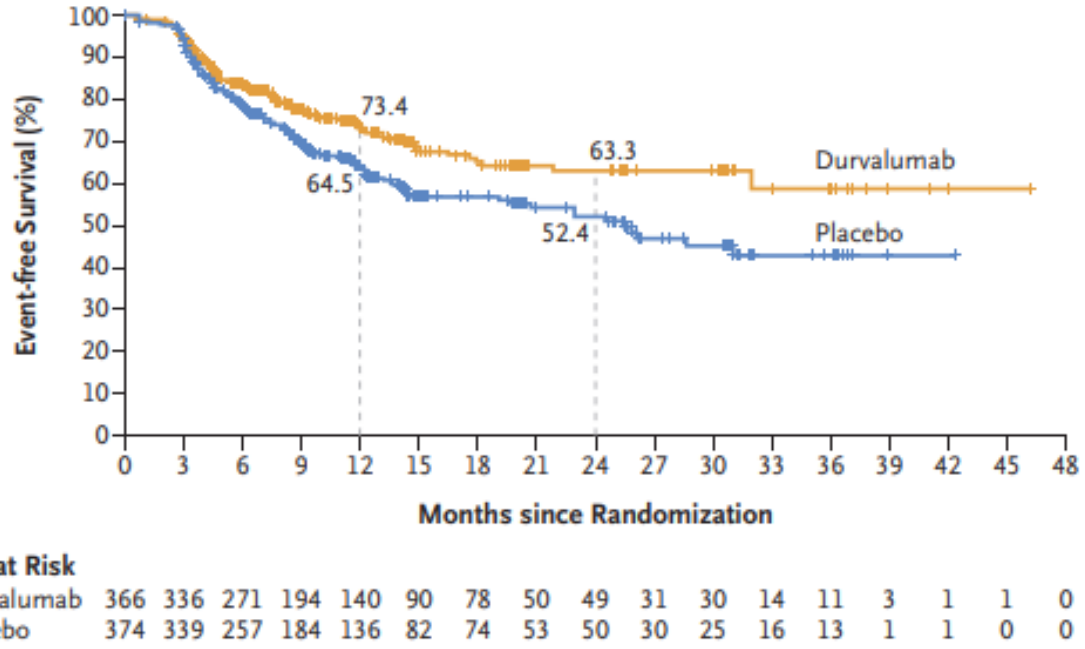
Figure 5. KM plot of EFS, mITT population



	No. of Events/ No. of Patients	Median Event-free Survival (95%CI)
		mo
Durvalumab	98/366 (26.8)	NR (31.9–NR)
Placebo	138/374 (36.9)	25.9 (18.9–NR)

Stratified hazard ratio for disease progression, recurrence, or death, 0.68 (95% CI, 0.53–0.88)
P=0.004 by stratified log-rank test

DCO 10 November 2022 (N=740)

Note: Durvalumab and placebo refers to the perioperative durvalumab and the perioperative placebo arms in AEGEAN

Abbreviations: CI, confidence interval; DCO, data cut-off; EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat; NR, not reached

Source: Heymach et al. 2023 [20]

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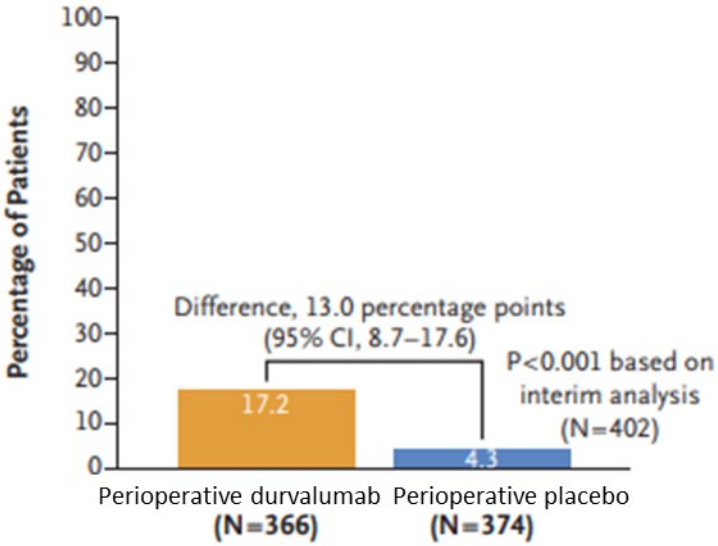
B.2.6.2 *Primary outcome: pCR*

The second primary outcome of AEGEAN, pCR, is an early indication of treatment efficacy and a stringent indication of response to treatment in the neoadjuvant setting.[69] In AEGEAN, pCR is defined as the proportion of patients who have a lack of any viable tumour cells after complete evaluation in the resected lung cancer specimen and all sampled regional lymph nodes.[20] Associations between pCR after neoadjuvant therapy and improvements in EFS and OS have been reported.[68,69] Several published SLRs and meta-analyses have demonstrated that pCR is indicative of survival benefit and therefore a suitable surrogate endpoint for OS in resectable NSCLC.[83-85] Due to the early nature of the resectable NSCLC and its improved prognosis versus metastatic disease, pCR is an endpoint that is highly relevant to patients with resectable NSCLC receiving neoadjuvant therapy. However, the potential impact of adjuvant therapy on long-term outcomes (EFS and OS) is not captured by pCR. As such, for the perioperative durvalumab regimen, EFS is considered more relevant to evaluate the full perioperative approach.

At the primary analysis of pCR (DCO 14 January 2022 [N=402]), all patients had been randomised for at least 7 months. Treatment with perioperative durvalumab resulted in a significant improvement in pCR compared with perioperative placebo. A higher pCR rate of 17.9% was observed for patients in the perioperative durvalumab arm versus 4.9% in the perioperative placebo arm. This resulted in a treatment difference in proportions of 13.0% (95% CI 7.1 to 19.5; p<0.001).[20,75]

The result for pCR at the final analysis (DCO 10 November 2022) was consistent with the pCR result at the primary analysis (DCO 14 January 2022) with a difference in proportions of 13.0% (95% CI 8.7 to 17.6) as shown in Figure 6.[20,75] At the time of the final analysis, the prespecified sensitivity analyses were consistent with the primary analysis results for pCR.[75]

Figure 6. pCR at final analysis, mITT population



DCO 10 November 2022 (N=740)

Abbreviations: CI, confidence interval; DCO, data cut-off; mITT, modified intention to treat; pCR, pathological complete response

Source: Heymach et al. 2023 [20]

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B.2.6.3 *Key secondary outcomes*

B.2.6.3.1 Overall survival

In AEGEAN, OS is defined as the time from randomisation to death.[75] Whilst still remaining a key clinical endpoint, the use of OS as an endpoint in early-stage NSCLC clinical trials is subject to a number of limitations.[86] A considerably longer trial follow-up period is required to collect OS data (e.g., median OS was not reached after three years in the preoperative arm of the NSCLC meta-analysis collaborative group analysis of neoadjuvant chemotherapy),[64] which could potentially delay patient access to treatment. Further, the measurement of OS can be confounded by the effects of subsequent therapies used in later lines following recurrence or progression.[86] For early-stage NSCLC therapies, other outcomes such as EFS that consider multiple patient-relevant events (disease progression precluding surgery, disease recurrence after surgery, and death) and that are also surrogate outcomes for OS, have more value in this setting.[80]

As per the MTP, OS was not formally tested for statistical significance at the primary analysis of EFS (DCO 10 November 2022) and median OS had not been reached for either treatment arm.[75] However, due to the importance of OS as a clinical outcome, a descriptive summary of the OS results at the November 2022 interim analysis and from the D120SU (DCO [redacted]), provided to the FDA and described in section B.2.3.2, is presented to support a NICE decision making.

At the primary analysis for EFS (DCO 10 November 2022), OS data had [redacted]% overall maturity, with [redacted] ([redacted]% for the perioperative durvalumab arm and [redacted]% for the perioperative placebo arm) with a HR of [redacted] (95% CI [redacted] to [redacted]) (Figure 7).[75] The median (range) of OS follow-up was [redacted] months in the perioperative durvalumab arm ([redacted]) and [redacted] ([redacted]) months for the perioperative placebo arm ([redacted]).[75]

Figure 7. KM plot of OS, mITT population

[redacted]

DCO 10 November 2022

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Note: Note: Durvalumab + SoC and placebo + SoC refers to the perioperative durvalumab and the perioperative placebo arms in AEGEAN

Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; KM, Kaplan-Meier; mITT, modified intention to treat; OS, overall survival; SoC, standard of care

Source: AstraZeneca 2023[75]

At the D120SU (DCO [redacted]), [redacted] was observed with a HR of [redacted] (95% CI [redacted] to [redacted]) (Table 15). This is [redacted] from the HR of [redacted] (95% CI [redacted] to [redacted]) at the primary analysis of EFS (DCO 10 November 2022). The subsequent DCO also shows [redacted] (Figure 8). [redacted]

Table 15. OS HR at D120SU

Summary of OS at D120SU	
HR (95% CI)	[redacted]
Maturity	[redacted]%
Median Follow up, months (range)	[redacted]

DCO [redacted]

Abbreviations: CI, confidence interval; D120SU, day 120 safety update; HR, hazard ratio; OS, overall survival

Source: AstraZeneca 2024[21]

Figure 8. KM plot of OS at D120SU

DCO [redacted]

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Note: Note: Durvalumab + SoC and placebo + SoC refers to the perioperative durvalumab and the perioperative placebo arms in AEGEAN

Abbreviations: CI, confidence interval; D120SU, day 120 safety update; DCO, data cut-off; KM, Kaplan-Meier; NC, not calculable; NR, not reached; OS, overall survival; SoC, standard of care

Source: AstraZeneca 2024[21]

Sensitivity analysis: Impact of deaths due to COVID-19 on OS

A pre-defined sensitivity analysis of OS was performed at DCO 10 November 2022. [redacted] patients who had a death reported to be due to COVID-19 were censored (using their death date as the censor date). Of the [redacted] death events, [redacted] events ([redacted] in the perioperative durvalumab arm and [redacted] in the perioperative placebo arm) occurred during the safety follow-up period and [redacted] events ([redacted]) occurred after the safety follow-up period.[75]

The censorship of these patients resulted in a HR of [redacted] (95% CI [redacted] to [redacted]) compared with [redacted] (95% CI [redacted] to [redacted]) for the main analysis conducted in the mITT population.[75]

At the D120SU the OS HR censoring COVID-19 deaths was [redacted] (95% CI [redacted] to [redacted]); [redacted] from [redacted] (95% CI: [redacted] to [redacted]) for the analysis conducted in the mITT population (DCO [redacted]).[21]

B.2.6.3.2 Major pathological response

Major pathologic response is defined as ≤10% viable tumour cells in lung primary tumour after complete evaluation in the resected lung cancer specimen[69,76,87,88], and has been proposed as a potential surrogate endpoint for OS following neoadjuvant chemotherapy in patients with NSCLC.[69] A study of 192 patients with resected NSCLC given neoadjuvant chemotherapy showed robust improvement in survival in patients with less than 10% viable tumour compared to those patients with more than 10% viable tumour (5-year OS 85% versus 40%, respectively).[87]

At the primary analysis (DCO 14 January 2022) there was a statistically significant improvement in MPR (per central pathological review) for patients in the perioperative durvalumab arm compared with those in the perioperative placebo arm (34.2% versus 14.1%, respectively) resulting in a significant difference in proportions of 20.1% (95% CI 11.8 to 28.3; p<0.001).[20]

The MPR findings at the final analysis (DCO 10 November 2022) were consistent with the primary analysis. The treatment difference in proportions for the perioperative durvalumab arm versus the perioperative placebo arm was 21.0% (33.3% versus 12.3%, respectively; 95% CI 15.1 to 26.9).[20]

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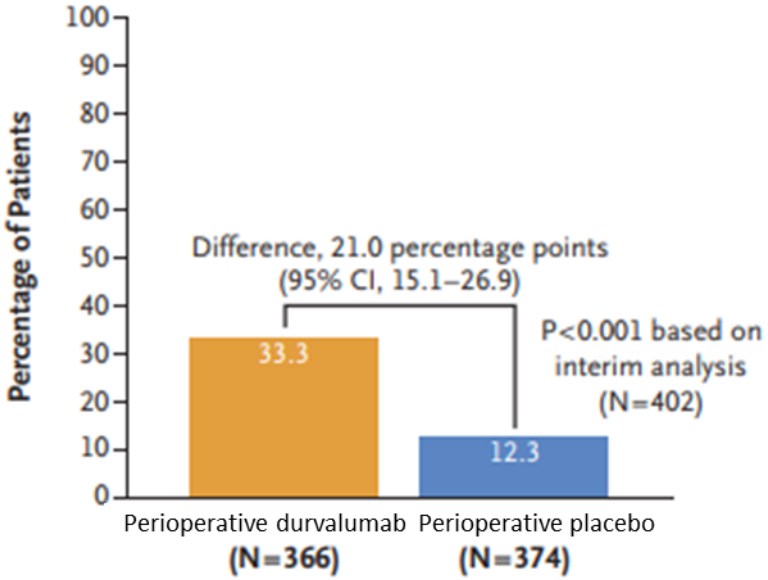
Figure 9. MPR at final analysis, mITT population



DCO 10 November 2022 (N=740)

Abbreviations: CI, confidence interval; DCO, data cut-off; mITT, modified intention to treat; MPR, major pathological response

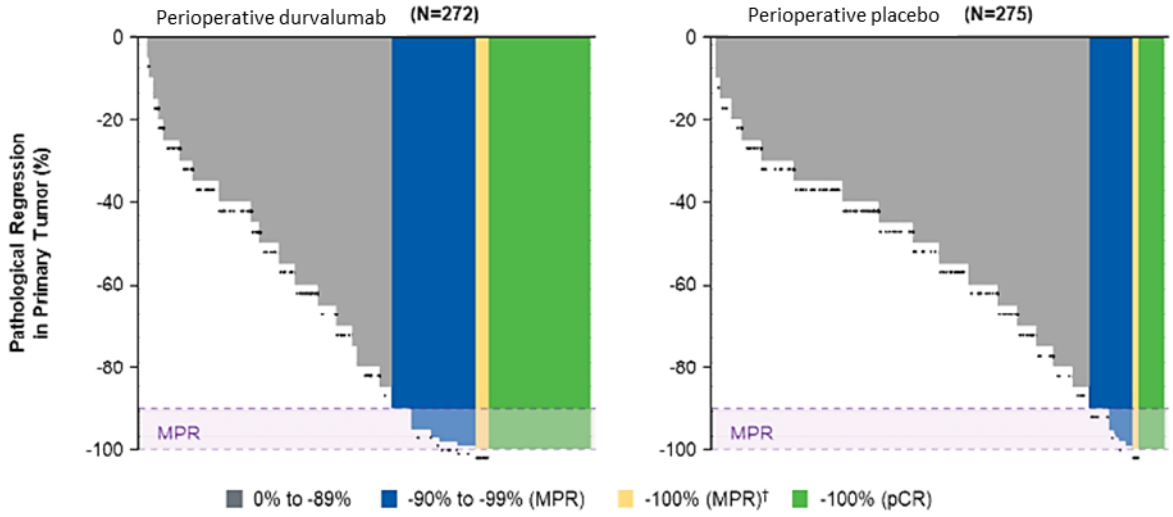
Source: Heymach et al. 2023 [20]

B.2.6.3.3 Pathological regression

Pathological regression of the primary tumour was evaluated in patients with evaluable percentage of residual viable tumour (RVT) and was defined as % viable tumour cells minus 100%.[20]

Patients in the perioperative durvalumab arm showed greater pathological regression of the primary tumour than patients in the perioperative placebo arm as demonstrated by the wider proportions of patients achieving MPR and pCR in the waterfall plot below (Figure 10).[20]

Figure 10. Pathological regression, mITT population



DCO 10 November 2022 (N=740). Pathological response was assessed using recommendations from the IASLC (2020).[76]

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Abbreviations: DCO, data cut-off; mITT, modified intention to treat; MPR, major pathological response; pCR, pathological complete response

*Indicates patients with evidence of carcinoma present in any examined lymph nodes or whose lymph nodes are not evaluable.

†Patients with no viable tumor cells in the primary tumor, but with evidence of carcinoma present in examined lymph nodes, or whose lymph nodes are not evaluable, are classified as responders for MPR and non-responders for pCR, in accordance with the definitions of these endpoints.

B.2.6.3.4 Objective response rate

The objective response rate (ORR), defined as the percentage of patients with a complete response or partial response at their latest assessment prior to surgery, was evaluated in the mITT population prior to surgery using BICR per RECIST v1.1 and was not a pre-defined study endpoint.[75] An analysis of ORR was performed to support pCR. More patients in the perioperative durvalumab arm achieved a complete or partial response than the perioperative placebo arm (56.3% and 38.0% respectively).[20]

Table 16. ORR prior to surgery (BICR RECIST v1.1), mITT population

Response	Perioperative durvalumab n=366	Perioperative placebo n=374
ORR, n (%) 95% CI	206 (56.3) 51.0-61.4	142 (38.0) 33.0-43.1
Patients with a response, n (%)		
Complete	4 (1.1)	1 (0.3)
Partial	202 (55.2)	141 (37.7)
No response, n (%)		
Stable disease	124 (33.9)	189 (50.5)
Progression	11 (3.0)	15 (4.0)
Not evaluable[a]	25 (6.8)	28 (7.5)

DCO 10 November 2022.

Abbreviations: CI, confidence interval; DCO, data cut-off; ORR, objective response rate

[a] Includes patients with missing baseline scans or missing pre-surgery scans

Source: Heymach et al. 2023[20]

B.2.6.4 *Health-related quality of life*

Health-related quality of life (HRQoL) was assessed using EQ-5D-5L in the mITT population at the primary analysis of EFS (DCO 10 November 2022). Only data in the neoadjuvant period (Week 12) were evaluated at the time of the primary analysis of EFS to preserve the integrity of study blinding for the DFS analysis. The evaluation of HRQoL for the adjuvant period (for both the resected set and the modified resected set) is ongoing and will be analysed at the same time as the DFS analyses.[75]

Overall compliance rates were high at neoadjuvant baseline ([redacted]) for the EQ-5D-5L analysis.[75] The compliance [redacted]% for the perioperative durvalumab arm and [redacted]% for the perioperative placebo arm at the adjuvant baseline visit (last on-treatment assessment of EQ-5D), with lower compliance at follow-up visits after discontinuation/completion of treatment.

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[redacted]

B.2.6.5 *Surgical outcomes*

The potential benefits of neoadjuvant immunotherapy include priming the immune system, preventing the growth and spread of micrometastases, and reducing the risk of disease recurrence.[66] However, it is important that neoadjuvant treatments do not result in delays to surgery with curative intent (as this may result in disease progression to an extent in which surgery can longer be performed) or increase the risk of surgical complications.[56]

In the neoadjuvant phase of AEGEAN, treatment with durvalumab + PDC did not adversely impact the feasibility or timing of surgery in the mITT population and resulted in a numerically higher rate of R0 resections.[20]

Table 17 summarises surgical outcomes in AEGEAN for the mITT population and shows a similar proportion of patients in the perioperative durvalumab and perioperative placebo arms completing surgery (77.6% and 76.7%, respectively).[20] Most patients were able to undergo R0 resection (94.7% in the perioperative durvalumab arm and 91.3% in the perioperative placebo).[20] A slightly higher number of patients experienced no delays to surgery in the perioperative durvalumab arm than the perioperative placebo arm; however, the median time from the last neoadjuvant treatment dose to surgery was the same for both treatment arms (34.0 days).[20] Of the patients that did experience a delay to surgery (perioperative durvalumab, 17.3% and perioperative placebo, 22.2%), most delays were less than 2 weeks in both treatment arms.[20]

Table 17. Summary of surgical outcomes, mITT population

Surgical outcome	Perioperative durvalumab n=366	Perioperative placebo n=374
Completed surgery		
Patients who underwent surgery, n (%)	295 (80.6)	302 (80.7)
Patients who completed surgery, n (%)	284 (77.6)	287 (76.7)
Days from last neoadjuvant treatment dose to surgery, median (range)[a]	34.0 (12–91)	34.0 (13–103)
Days from surgery to first dose of adjuvant treatment, median (range)[b]	50.0 (22–136)	52.0 (21–141)
Resection		
R0	269 (94.7)	262 (91.3)
R1	12 (4.2)	22 (7.7)
Surgical delay		
No surgical delay, n (%)	244 (82.7)	235 (77.8)
Any surgical delay, n (%)	51 (17.3)	67 (22.2)
Duration of delay		
<2 weeks	28 (9.5)	38 (12.6)

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2 to <4 weeks	12 (4.1)	22 (7.3)
4 to <6 weeks	7 (2.4)	3 (1.0)
≥6 weeks	4 (1.4)	4 (1.3)

DCO 10 November 2022 (N=740)

Abbreviations: DCO, data cut-off; mITT, modified intention to treat

[a] Based on the number of patients who underwent surgery (perioperative durvalumab arm, n=295; perioperative placebo arm, n=279)

[b] Based on the number of patients in the modified intent-to-treat population who started adjuvant treatment (perioperative durvalumab arm, n=241; perioperative placebo arm, n=237)

Source: Heymach et al. 2023[20]; Mitsudomi 2023[89]

B.2.7 *Subgroup analysis*

Prespecified subgroup analyses were performed for the EFS and pCR primary outcomes. The focus of the subgroup assessment was to assess the extent to which the overall observed treatment effect was consistent across individual subgroups. The lower number of patients and events across the individual subgroups leads to greater uncertainty in their point estimates and wider CIs. No adjustments were made for multiplicity.[75]

B.2.7.1 *Subgroup analysis for EFS*

At the primary analysis of EFS (DCO 10 November 2022), all subgroup analyses for age, sex, ECOG PS, race, geographic region, smoking history, histology, disease stage, lymph node station, PD-L1 expression, and planned neoadjuvant platinum agent, favoured the perioperative durvalumab arm (all HR<1) (Figure 11).[20]

For PD-L1 expression <1% at baseline and disease stage, the HRs fall within the 95% CI for the mITT population (grey shaded column in Figure 11) indicating EFS improvements in these subgroups are consistent with the overall EFS improvement seen in the mITT population.[20] The lower number of patients and events across the individual subgroups leads to greater uncertainty and wider CIs around the point estimates.

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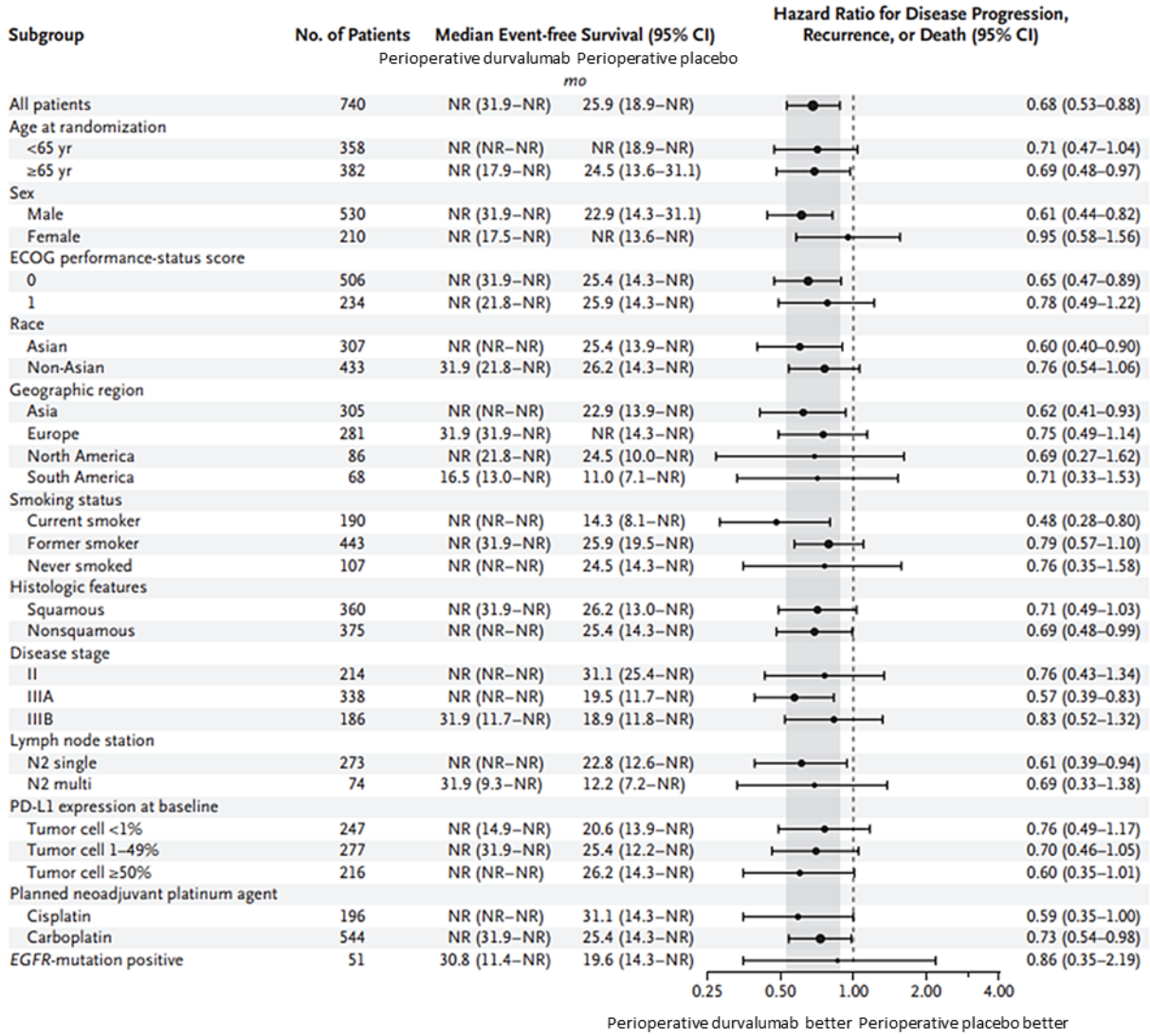
Figure 11. Subgroup analyses of EFS (BICR using RECIST 1.1), mITT population



DCO 10 November 2022 (N=740). The 95% CIs were estimated using a stratified Miettinen and Nurminen method for all patients (mITT) and an unstratified Miettinen and Nurminen method for subgroups. The size of the data point is proportional to the number of patients for each subgroup, and the horizontal bars represent the 95% CIs. Shading indicates the HR and 95% CI for EFS in the mITT population.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group, EFS, event-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; mITT, modified intention to treat; NR, not reached; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumours

*Race was self-reported per electronic case report form.

†Determined using the Ventana SP263 immunohistochemistry assay

Source: Heymach et al. 2023[20]; AstraZeneca 2023[75]

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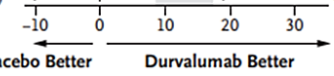
B.2.7.2 *Subgroup analysis for pCR*

At the final analysis of pCR (DCO 10 November 2022), all subgroup analyses for age, sex, ECOG PS, race, geographic region, smoking history, histology, disease stage, lymph node station, PD-L1 expression, planned neoadjuvant platinum agent, and EGFR mutation status favoured the perioperative durvalumab arm (Figure 12).[20]

Figure 12. Subgroup analysis of pCR, mITT population

Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Difference in Pathological Complete Response (95% CI)
		Durvalumab	Placebo	
		percent		*percentage points*
All patients	740	17.2 (13.5 to 21.5)	4.3 (2.5 to 6.9)	13.0 (8.7 to 17.6)
Age at randomization				
<65 yr	358	18.3 (12.9 to 24.8)	3.8 (1.6 to 7.7)	14.5 (8.3 to 21.3)
≥65 yr	382	16.2 (11.3 to 22.2)	4.7 (2.2 to 8.8)	11.5 (5.6 to 17.9)
Sex				
Male	530	19.4 (14.7 to 24.9)	4.7 (2.5 to 7.9)	14.8 (9.5 to 20.5)
Female	210	12.3 (6.9 to 19.7)	3.1 (0.6 to 8.9)	9.2 (2.0 to 16.9)
ECOG performance-status score				
0	506	16.7 (12.3 to 21.9)	5.1 (2.7 to 8.6)	11.6 (6.4 to 17.3)
1	234	18.3 (11.7 to 26.5)	2.5 (0.5 to 7.2)	15.7 (8.6 to 24.1)
Race				
Asian	307	18.2 (12.2 to 25.5)	4.3 (1.7 to 8.6)	13.9 (7.2 to 21.5)
Non-Asian	433	16.6 (12.0 to 22.1)	4.3 (2.0 to 8.0)	12.3 (6.8 to 18.2)
Geographic region				
Asia	305	18.3 (12.3 to 25.7)	4.3 (1.7 to 8.6)	14.0 (7.2 to 21.7)
Europe	281	19.9 (13.6 to 27.4)	5.0 (2.0 to 10.0)	14.9 (7.5 to 22.8)
North America	86	14.0 (5.3 to 27.9)	2.3 (0.1 to 12.3)	11.6 (0.0 to 25.4)
South America	68	7.5 (1.6 to 20.4)	3.6 (0.1 to 18.3)	3.9 (−11.2 to 17.1)
Smoking status				
Current smoker	190	24.2 (16.0 to 34.1)	4.2 (1.2 to 10.4)	20.0 (10.7 to 30.1)
Former smoker	443	17.3 (12.5 to 22.9)	5.4 (2.8 to 9.2)	11.9 (6.2 to 18.0)
Never smoked	107	3.9 (0.5 to 13.5)	0.0 (0.0 to 6.4)	3.9 (−2.7 to 13.3)
Histology				
Squamous	360	21.3 (15.4 to 28.3)	5.2 (2.5 to 9.4)	16.1 (9.3 to 23.4)
Nonsquamous	375	13.3 (8.9 to 18.8)	3.4 (1.2 to 7.2)	9.9 (4.6 to 15.8)
Disease stage				
II	214	21.2 (13.8 to 30.3)	4.5 (1.5 to 10.3)	16.6 (8.1 to 26.0)
IIIA	338	18.5 (13.0 to 25.1)	4.8 (2.1 to 9.3)	13.6 (7.1 to 20.7)
IIIB	186	10.2 (4.8 to 18.5)	3.1 (0.6 to 8.7)	7.2 (0.1 to 15.7)
Lymph node station				
N2 single	273	18.4 (12.4 to 25.8)	4.5 (1.7 to 9.6)	13.9 (6.6 to 21.7)
N2 multi	74	8.8 (1.9 to 23.7)	5.0 (0.6 to 16.9)	3.8 (−9.2 to 18.8)
PD-L1 expression at baseline				
Tumor cell <1%	247	9.0 (4.6 to 15.6)	3.2 (0.9 to 8.0)	5.8 (−0.2 to 12.7)
Tumor cell 1–49%	277	16.3 (10.5 to 23.6)	4.9 (2.0 to 9.9)	11.4 (4.3 to 19.1)
Tumor cell ≥50%	216	27.5 (19.4 to 36.9)	4.7 (1.5 to 10.6)	22.9 (13.7 to 32.5)
Planned neoadjuvant platinum agent				
Cisplatin	196	12.0 (6.4 to 20.0)	2.1 (0.3 to 7.3)	9.9 (3.1 to 18.0)
Carboplatin	544	19.2 (14.6 to 24.4)	5.0 (2.8 to 8.3)	14.1 (8.9 to 19.8)
EGFR-mutation positive	51	3.8 (0.1 to 19.6)	0.0 (0.0 to 13.7)	3.8 (−10.0 to 19.1)



DCO 10 November 2022. The 95% CIs were estimated using a stratified Miettinen and Nurminen method for all patients (mITT) and an unstratified Miettinen and Nurminen method for subgroups. The size of the data points is proportional to the number of patients for each subgroup, and the horizontal bars represent the 95% CIs. Shading indicates the HR and 95% CI for pCR in the mITT population.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; mITT, modified intention to treat; NR, not reached; pCR, pathological complete response; PD-L1, programmed cell death ligand-1

*Race was self-reported per electronic case report form.

†Determined using the Ventana SP263 immunohistochemistry assay

Source: Heymach et al. 2023[20]; AstraZeneca 2023[75]

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B.2.8 *Meta-analysis*

Only one trial (AEGEAN) evaluating perioperative durvalumab for the treatment of resectable NSCLC was identified in the SLR, thus a meta-analysis could not be conducted.

B.2.9 *Indirect and mixed treatment comparisons*

In AEGEAN, perioperative durvalumab + neoadjuvant PDC was compared against perioperative placebo + neoadjuvant PDC. In clinical practice, the treatment options for patients include neoadjuvant nivolumab + PDC, adjuvant PDC, or surgery alone.[3] In the absence of direct comparative data for perioperative durvalumab versus these comparators, ITCs have been performed for the primary outcome of interest, EFS. Full details of the SLR to identify relevant studies for the ITCs are presented in Appendix D.1.

A feasibility assessment was conducted to compare the design, population, and outcome definitions between the selected studies of interest. Effect modifiers were also considered. This is described in full in Appendix D.2. Based on the available evidence identified in the SLR and feasibility of networks, it was concluded that the most appropriate methods to compare perioperative durvalumab with the relevant comparators were anchored population-adjusted indirect comparison (PAIC) and network meta-analysis (NMA).

All ITC 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. The piecewise approach was explored due to the delayed separation of the perioperative durvalumab and neoadjuvant PDC EFS curves in the AEGEAN trial (Figure 5). The time intervals for the piecewise analysis align with both the timing of the separation and the first planned tumour assessment in the AEGEAN trial. Compared with the overall follow-up period (from time = 0 months), the piecewise analysis of EFS (from time = 3 months) shows evidence of proportionality, with parallel curves observed across the follow-up period for the 3+ months time interval in the log-cumulative hazard plot (see Appendix D.2.1.6).

Two ITCs were conducted:

- An anchored matching-adjusted indirect comparison (MAIC) to compare perioperative durvalumab (AEGEAN[20]) with neoadjuvant nivolumab + PDC (CheckMate 816[66]).
- An NMA to compare perioperative durvalumab versus adjuvant PDC and versus surgery alone.

B.2.9.1 *MAIC versus neoadjuvant nivolumab*

Anchored MAIC analyses were performed to compare the efficacy of perioperative durvalumab from AEGEAN[20] with neoadjuvant nivolumab + PDC from CheckMate 816[66] 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 PAIC approach when there is evidence of imbalances in possible effect modifiers across trials.[90]

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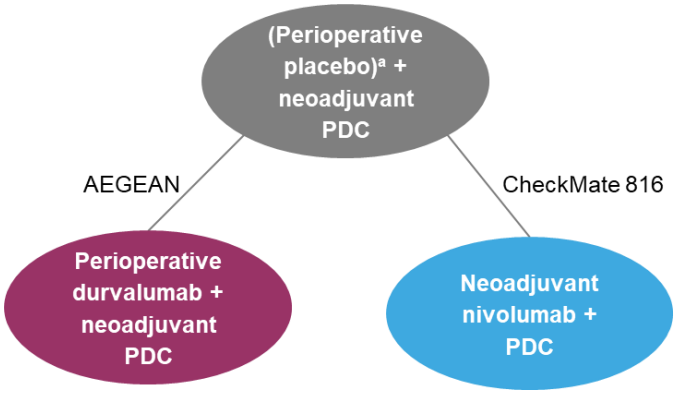
Analyses for the MAIC were conducted utilising the mITT population in AEGEAN.[20] Figure 13 shows the network of evidence utilised.

Figure 13. Anchored PAIC diagram for AEGEAN versus CheckMate 816



Abbreviations: PAIC, population-adjusted indirect comparison; PDC, platinum-doublet chemotherapy
[a] There is no placebo in CheckMate 816

The full methods and data inputs for the MAIC are reported in Appendix D.2.2. Analyses for the MAIC were conducted using R version 4.1.0 within the R Studio environment. Packages used included maic (v 0.1.4), survival (v 3.4.0) and survminer (v 0.4.9).

The baseline characteristics that were considered possible effect modifiers for ITCs included: disease stage, PD-L1 expression, histology, region (Asia versus non-Asia), sex, smoking status, and planned platinum chemotherapy (Appendix D.2.1.1). Upon comparison of baseline characteristics between AEGEAN and CheckMate-816, imbalances (5% or more) between trials were observed in: the proportion of patients with cisplatin as planned chemotherapy at baseline, proportion with stage IIIA at baseline, proportion with stage IIIB at baseline, proportion of Asian patients enrolled (region), and proportion with PD-L1 <1%. Effect modifiers were discussed with UK clinical experts and the general consensus was that all baseline characteristics could be possible effect modifiers; however, some would have a stronger impact on EFS than others.[22]

Based on the variables to be included in the MAIC, propensity score weighting was used to derive weights for individual patients in the AEGEAN trial.[91] These weights aimed to balance or adjust the baseline characteristics of participants so that, after applying these weights, the average characteristics of the AEGEAN population matched the published aggregate characteristics of the CheckMate 816 population.

In line with recommendations in NICE DSU TSD 18,[90] the base case analysis for the MAIC included all possible effect modifiers in the weighting, regardless of whether these were imbalanced or not (i.e. disease stage (IIIB versus other; IIIA versus other), PD-L1 expression (<50% versus ≥50%; <1% versus ≥1%), histology, region (Asia vs non-Asia), sex, smoking status, and planned platinum chemotherapy were included as variables for weighting in the base case analysis). Additionally, a scenario analysis was conducted to explore the impact on results of only weighting for those characteristics that were imbalanced between trials

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(i.e. disease stage, PD-L1 expression, region, and planned platinum chemotherapy included in the weighting).

After weighting, the baseline characteristics in AEGEAN matched those in CheckMate 816 for those variables that were included in the weighting (see Appendix D.2.2.2, Table 32). In the additional scenario, weighting resulted in an increase in the proportion of patients with non-squamous histology and the proportion of patients who had never smoked, introducing imbalances between AEGEAN and CheckMate 816 in these baseline characteristics, both of which are considered possible effect modifiers (see Appendix D.2.2.2, Table 33). This further supports the inclusion of all possible effect modifiers in the base case analysis.

The effective sample size (ESS) in AEGEAN after weighting to CheckMate 816 in each scenario is shown in Table 18 along with information about the distribution of weights in Appendix D.2.2.2, Figure 6.

Table 18. ESS of AEGEAN (weighted to match CheckMate 816) in the base case and scenario 1

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]

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 19. In both 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 19. Cox regression analysis of EFS for perioperative durvalumab versus perioperative placebo in AEGEAN (unweighted and after weighting in the base case and scenario 1)

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]

Based on the unstratified Cox proportional hazard model.

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Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18:[90] 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

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 (see Appendix D.2.2.3). Event numbers before weighting for 0-to-3-months and 3+ months time intervals are presented in Appendix D.2.2.3, Table 36. The results for the piecewise Cox regression analysis of EFS for perioperative durvalumab versus perioperative placebo in AEGEAN (unweighted and after weighting in the base case and scenario 1) and for neoadjuvant nivolumab versus PDC in CheckMate 816 are presented in Appendix D.2.2.3, Table 37.

B.2.9.1.1 Results

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 ([redacted]), with an EFS HR of [redacted] (95% CI [redacted] to [redacted]) (Table 20).

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

Table 20. MAIC EFS HRs for perioperative durvalumab versus neoadjuvant nivolumab + PDC (unweighted and after weighting in the base case and scenario 1)

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]

Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18:[90]: 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

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

The results of the piecewise analyses are shown in Table 21. The robustness of the piecewise MAIC results for the 0-to-3-month time interval is limited by a low number of events occurring in each trial across treatment arms ([redacted]; see Appendix D.2.2.3, Table 36) in this time period. Although the base case and scenario 1 HRs were in favour of perioperative durvalumab, due to this limitation and the absence of a clear separation of EFS curves in the trials, caution is advised in interpreting the results of the analyses for this time interval.[20,66]

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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 [redacted]. After weighting, improvements in EFS (3+ months) were estimated for perioperative durvalumab versus neoadjuvant nivolumab + PDC ([redacted]), with an EFS HR of [redacted] (95% CI [redacted]), in the base case analysis, and [redacted] (95% CI [redacted], [redacted] in scenario 1.

Table 21. 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 1)

		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]

Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD 18:[90]: 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

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

B.2.9.2 *NMA versus adjuvant PDC and surgery alone*

An NMA was conducted to compare perioperative durvalumab versus adjuvant PDC and versus surgery alone. This approach was taken to include evidence from the multiple studies identified in the SLR and in the absence of clear candidates amongst these trials for conducting pairwise MAICs. Use of NMA for these comparisons is also consistent with the approach taken in NICE TA876.[50] Sensitivity analyses were conducted to explore removal of studies likely to introduce heterogeneity (disease stage, second generation [2G] versus third generation [3G] chemotherapy, and region).

The EFS HR data were analysed using NMA for the mITT population of AEGEAN. 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 full NMA methods are reported in Appendix D.2.3 and summarised below.

The NMA was conducted in a Bayesian framework, using Monte Carlo Markov Chain simulation methods, and using R version 4.0.2.[92] Both fixed- and random-effects models were considered and model fit was assessed based on deviance information criteria (DIC). Given the level of heterogeneity identified in the feasibility assessment, the random-effects models were preferred, with the fixed-effects models provided for completeness. With limited data to estimate between-study heterogeneity for random-effects models, 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.[93]

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The base case analysis synthesised evidence from all relevant studies included in the feasibility assessment. Sensitivity analyses were carried out to assess the impact on NMA results of differences between the comparator studies and versus AEGEAN, e.g., by excluding studies that included second-generation (2G) chemotherapy regimens, and/or Asia-only trials, and/or studies with clear differences in disease stage. For the piecewise analyses, the EFS KM curves from comparator trials were digitised and the survSplit function in R was used to split the pseudo-patient level data into respective 0 to 3 months and 3+ months timepoints, through the creation of an indicator variable denoting timepoint. A Cox regression model with an interaction between the timepoint indicator variable and treatment was then used to obtain an estimate of the timepoint-specific (piecewise) HRs.

The network of evidence for the base case analysis versus adjuvant PDC and surgery alone is shown in Figure 14. The corresponding study sizes and number of events, including the time intervals used for piecewise analyses, can be found in Appendix D.2.3.2 (Table 40). Due to the low number of events in the 0-to-3-month time interval across studies (with some studies reporting zero events), the models did not converge, therefore a piecewise NMA was not feasible for this time interval. Given this, results are only presented for the piecewise NMA using the 3+ month time interval.

The HRs and associated 95% CIs that were used for inputs in the NMA are presented in Appendix D.2.3.2, Table 41 (overall period) and Table 42 (piecewise 3+ months). Table 22 lists the studies excluded for each sensitivity analysis. In Rosell 1994, the sample size (n=30 in each arm) were much smaller than many of the other studies informing comparisons between surgery alone and neoadjuvant PDC and it had the largest effect size for this comparison. The sample size in Li 2009 (n=28 in each arm) was also much smaller than other studies, and the effect size reported in this study was also higher than the other 'surgery alone' studies (albeit not as high as Rosell 1994).

Heterogeneity, (I^2 values) for the overall period and 3+ months of the mITT population are presented in Table 23. For the NMA in the overall period, the I^2 value in the overall NMA shows significant heterogeneity (>75%) among studies that inform the comparison between surgery alone and neoadjuvant PDC in both the base case analysis and sensitivity analysis 3 (which both include Rosell 1994). Heterogeneity was reduced in other sensitivity analyses, with the lowest I^2 in sensitivity analysis 2, which excluded both Rosell 1994 and Li 2009.

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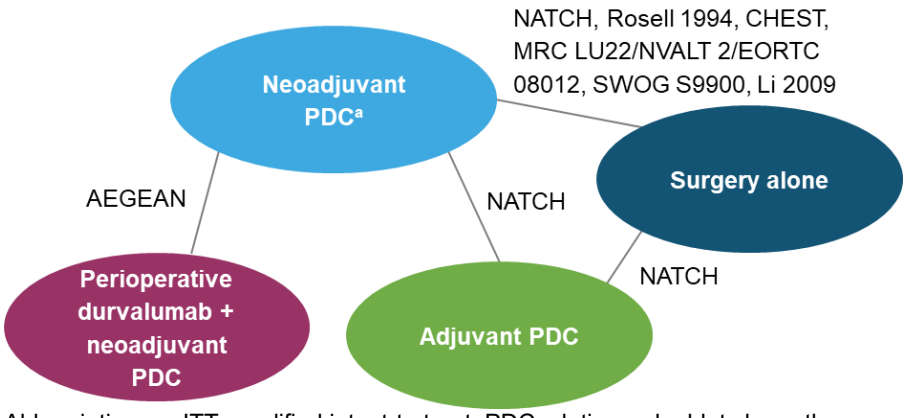
Figure 14. Network diagram of mITT AEGEAN versus adjuvant PDC and surgery alone, base case



Abbreviations: mITT, modified intent-to treat; PDC, platinum-doublet chemotherapy

[a] In AEGEAN, placebo + PDC was the neoadjuvant PDC arm

Table 22. List of studies excluded from mITT population sensitivity analyses

Population	Analysis	Description	Reason for exclusion in sensitivity analysis
mITT	Base case	All studies	NA
mITT	Sensitivity analysis 1	Excludes Rosell 1994,[94] MRC LU/22/NVALT 2/EORTC 09012[94]	Exclude studies with 2G chemotherapy
mITT	Sensitivity analysis 2	Excludes Rosell 1994,[95,96] Li 2009[97]	Exclude studies with stage III patients only
mITT	Sensitivity analysis 3	Excludes Li 2009[97]	Exclude Asia only studies
mITT	Sensitivity analysis 4	Excludes Rosell 1994,[94] MRC LU/22/NVALT 2/EORTC 09012,[94] Li 2009[97]	Exclude studies for any of the reasons above

Abbreviation: 2G, second generation; mITT, modified intent-to-treat; NA, not applicable

Table 23. Heterogeneity (I^2) in the mITT population network (overall period and 3+ months piecewise)

Population	Comparison	Analysis	I^2 overall period	I^2 3+ months piecewise
mITT	Surgery alone versus Neoadjuvant PDC	Base case	[redacted]%	[redacted]%
		Sensitivity analysis 1	[redacted]%	[redacted]%
		Sensitivity analysis 2	[redacted]%	[redacted]%
		Sensitivity analysis 3	[redacted]%	[redacted]%
		Sensitivity analysis 4	[redacted]%	[redacted]%

Abbreviations: mITT, modified intent-to-treat; neoadj, neoadjuvant; PDC, platinum-doublet chemotherapy; SA, sensitivity analysis

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B.2.9.2.1 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 Appendix D.2.3.3. As noted earlier, the random-effects models were preferred given the level of heterogeneity identified in the feasibility assessment. Except for the base case and sensitivity analysis 3 (both of which included Rosell 1994, where the DIC were lower for random effects models), the DIC values were similar between fixed- and random-effects models in the overall period.

The HRs, including 95% 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 15 (base case) and Figure 15 to Figure 19 (sensitivity analyses).

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% credible interval [CrI] <1).

There were wide 95% CrIs in the random-effects model that included Rosell 1994 (base case and sensitivity analysis 3), which was a small study with a large effect. In random effects models, smaller studies were assigned relatively more weight, which can lead to differences in the estimated effect size between random- and fixed effect models if these small studies reported a treatment effect that is different from other studies (as is the case with Rosell 1994 in this network). Also, given the importance of stage as a possible effect modifier, sensitivity analysis (excluding studies only in stage III), may represent a plausible alternative estimate.

Across the sensitivity analyses, a consistent survival benefit in favour of perioperative durvalumab was observed. The results of sensitivity analysis 2 were associated with greater precision (narrower 95% CrIs) and as a result of excluding Rosell 1994 and Li 2009, statistical heterogeneity (I^2) was reduced from [redacted]% in the base case analysis to [redacted]% in sensitivity analysis 2. The EFS HRs from the random effects NMA sensitivity analysis 2 in the overall period were [redacted] (95% CrI [redacted] to [redacted], [redacted] (95% CrI [redacted] to [redacted]) and [redacted] (95% CrI [redacted] to [redacted]) for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC and surgery alone, respectively. The results of sensitivity analysis 2 were used as estimates of relative efficacy in the cost-effectiveness model.

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Figure 15. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (base case)

Base case = all studies included

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

Figure 16. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 1)

Sensitivity analysis 1 = Excludes Rosell 1994,[95,98,99] MRC LU/22/NVALT 2/EORTC 09012[94] (studies with 2G PDC)

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

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Figure 17. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 2)

Sensitivity analysis 2 = Excludes Rosell 1994,[95,98,99] Li 2009[97] (studies with stage III patients only)

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

Figure 18. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 3)

Sensitivity analysis 3 = Excludes Li 2009[97] (Asia only studies)

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

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Figure 19. EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 4)

Sensitivity analysis 4 = Excludes Rosell 1994,[95,98,99] MRC LU/22/NVALT 2/EORTC 09012,[94] Li 2009[97] (studies with 2G PDC, studies with stage III only patients, and Asia-only studies)

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

B.2.10 *Adverse reactions*

B.2.10.1 *Exposure*

Overall, the median actual duration of exposure to perioperative durvalumab or perioperative placebo at the primary EFS analysis (DCO 10 November 22) was comparable in both treatment arms (32.00 weeks for the perioperative durvalumab arm versus 28.36 weeks for the perioperative placebo arm) and was sufficient for evaluating both the safety and tolerability of perioperative durvalumab.[75] In the neoadjuvant period, the median total duration of exposure was the same in both arms and the same for both durvalumab/placebo and chemotherapy (12.1 weeks).[20].

The combination of perioperative durvalumab with neoadjuvant PDC did not affect patients' ability to undergo 4 cycles of any chemotherapy. The proportion of patients who completed four cycles of neoadjuvant PDC in the perioperative durvalumab and perioperative placebo arms were 84.7% and 87.2%, respectively.[20] Similar proportions of patients in both treatment arms completed four cycles of durvalumab or placebo in the neoadjuvant phase (86.9% and 88.5%, respectively).[20]

The study protocol allowed patients to switch from cisplatin to carboplatin therapy in the event of unfavourable tolerability.[75] Overall, 26 patients switched platinum-based chemotherapy (24 patients switched from cisplatin to carboplatin as permitted by the protocol and 2 patients had off-protocol switching from carboplatin to cisplatin).[75] In addition, 6 patients had off-protocol switching of non-platinum chemotherapy (5 patients switched from paclitaxel to gemcitabine and 1 patient switched from pemetrexed to paclitaxel)[75] The switching means that the number of patients receiving 4 cycles of cisplatin is lower than the reported planned neoadjuvant platinum agent at baseline.

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In the adjuvant period, the median total duration of exposure was longer for durvalumab (37.14 weeks) than for placebo (34.43 weeks). The proportion of patients who received treatment for a period of ≥28 weeks was 41.9% and 37.9% for the perioperative durvalumab and perioperative placebo arms, respectively.[75]

B.2.10.2 *Adverse event overview*

The assessment of safety of perioperative durvalumab is based on the safety analysis population (n=799) at DCO 10 November 2022.[74] The post-surgical adverse event assessment was based on those patients in the modified safety analysis population who underwent surgery (n=597).[89]

In summary, perioperative durvalumab + neoadjuvant PDC was well-tolerated with manageable adverse events (AEs).[74] There was no increase in frequency or severity of AEs when durvalumab was used in combination with neoadjuvant PDC compared with perioperative placebo + neoadjuvant PDC, and the safety profile of neoadjuvant durvalumab + neoadjuvant PDC followed by adjuvant durvalumab post-surgery was consistent with the known safety profiles of each agent.[20]

Table 24 presents a summary of any grade AEs that were reported in the AEGEAN safety analysis population. Any cause grade 3 or 4 AEs were similar for the perioperative durvalumab and perioperative placebo arms (42.4% and 43.2%, respectively).[20] Deaths that occurred in each arm were not considered to be related to study treatment in most cases. Immune-mediated AEs of any grade were reported in 23.7% of patients in the perioperative durvalumab arm and 9.3% of patients in the perioperative placebo arm. Most were grade 1 or 2 adverse events, with grade 3 or 4 immune-mediated AEs reported in 4.2% and 2.5%, respectively, in the two arms.[20] Treatment discontinuations were higher in the perioperative durvalumab arm compared to the perioperative placebo arm in the neoadjuvant period, due to discontinuations resulting from two active agents (durvalumab and PDC).[20]

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Table 24. Summary of any grade AEs in AEGEAN in the overall study period, safety analysis set

Overall study period	Perioperative durvalumab (n=401)	Perioperative placebo (n=398)
AEs of any grade and any cause, n (%)	**387 (96.5)**	**377 (94.7)**
Maximum grade 3 or 4	170 (42.4)	172 (43.2)
Serious adverse events	151 (37.7)	125 (31.4)
Events leading to death	23 (5.7)	15 (3.8)
Leading to discontinuation of durvalumab or placebo	48 (12.0)	24 (6.0)
Leading to cancellation of surgery	7 (1.7)	4 (1.0)
AEs of any grade possibly related to durvalumab, placebo or chemotherapy, n (%)	**348 (86.8)**	**321 (80.7)**
Maximum grade 3 or 4	130 (32.4)	131 (32.9)
Events leading to death[b]	7 (1.7)	2 (0.5)
Any immune-related AE	**95 (23.7)**	**37 (9.3)**
Any grade 3 or 4	17 (4.2)	10 (2.5)

DCO 10 November 2022 (n=799)

Abbreviations: AE, adverse events; DCO, data cut-off

[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 plus 90 days, the data-cutoff date, or the date of the first dose of subsequent anti-cancer treatment.

[b] Adverse events 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, hemoptysis, myocarditis, and decreased appetite (one patient each) in the durvalumab group and pneumonia and infection (one patient each) in the perioperative placebo group.

Source: Heymach et al. 2023[20]

The most common AEs experienced by patients in the perioperative durvalumab arm were anaemia (34.0%), nausea (25.3%), and constipation (24.8%) (Table 25).[20] These three most frequently reported AEs are consistent with known toxicities of chemotherapy (gastrointestinal and blood/lymphatic disorders).[100,101] Rash, pruritis, and hypothyroidism were AEs that were reported at a rate of >5% higher in the perioperative durvalumab arm versus the perioperative placebo and all are consistent with the known safety profile of durvalumab.[102]

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Table 25. Summary of most common AEs in AEGEAN (overall study period), safety analysis set[a]

AEs, n (%)	Perioperative durvalumab (n=401)		Perioperative placebo (n=398)	
	Any grade	Maximum Grade 3 or 4	Any grade	Maximum Grade 3 or 4
Anaemia	136 (33.9)	26 (6.5)	126 (31.7)	26 (6.5)
Nausea	101 (25.2)	1 (0.2)	115 (28.9)	1 (0.3)
Constipation	100 (24.9)	1 (0.2)	84 (21.1)	0
Decreased appetite[b]	73 (18.2)	1 (0.2)	70 (17.6)	1 (0.3)
Alopecia	69 (17.2)	0	63 (15.8)	1 (0.3)
Neutropenia	68 (17.0)	36 (9.0)	71 (17.8)	38 (9.5)
Neutrophil count decreased	64 (16.0)	39 (9.7)	57 (14.3)	43 (10.8)
Rash	56 (14.0)	2 (0.5)	34 (8.5)	1 (0.3)
Diarrhoea	52 (13.0)	3 (0.7)	49 (12.3)	3 (0.8)
Fatigue	52 (13.0)	0	46 (11.6)	1 (0.3)
Asthenia	50 (12.5)	0	54 (13.6)	5 (1.3)
Pruritus	47 (11.7)	1 (0.2)	22 (5.5)	0
Vomiting	45 (11.2)	3 (0.7)	42 (10.6)	4 (1.0)
COVID-19[c]	45 (11.2)	1 (0.2)	35 (8.8)	3 (0.8)
Procedural pain	44 (11.0)	1 (0.2)	48 (12.1)	2 (0.5)
Insomnia	41 (10.2)	0	46 (11.6)	0

DCO 10 November 2022 (n=799)

[a] The safety analysis set includes all randomised patients who received at least one dose of study treatment; one patient assigned to the perioperative placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the perioperative durvalumab arm for the safety analysis set; adverse events were graded using Common Terminology Criteria for Adverse Events version 5.0. Included are adverse events reported with an any-grade incidence of at least 10% in the perioperative durvalumab arm during the overall study period, which spans from the first dose of study treatment (durvalumab or placebo or chemotherapy) until the earliest of: the last dose of study treatment or surgery + 90 days (taking the latest dose of durvalumab or placebo or chemotherapy or the date of surgery, + 90 days); the data cut-off date; or the date of the first dose of subsequent anti-cancer treatment.

[b] Two patients (one in each arm) had decreased appetite with an outcome of death (max. grade 5); the fatal event in the perioperative durvalumab arm was assessed as possibly related to study treatment by the investigator.

[c] Six patients had COVID-19 events of maximum grade 5 (perioperative durvalumab arm, n=5; perioperative placebo arm, n=1); all COVID-19 deaths were assessed by the investigator as unrelated to study treatment (note: COVID-19 is summarised as a grouped term comprising the 'COVID-19' and 'COVID-19 pneumonia' adverse event preferred terms).

Abbreviations: AE, adverse events; DCO, data cut-off

Source: Heymach et al. 2023[20]

Perioperative durvalumab + neoadjuvant PDC also did not affect the proportion of patients with any grade AEs possibly related to surgery, or with any surgical complication (Table 26).[89]

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Table 26. Summary of AEs possibly related to surgery and surgical complications in AEGEAN (post-surgery period), underwent surgery, modified safety analysis set

Post-surgery period[a]	Perioperative durvalumab (N=296)	Perioperative placebo (N=301)
Any grade AEs possibly related to surgery, n (%)[b]	119 (40.2)	118 (39.2)
Max. grade 3 or 4	25 (8.4)	28 (9.3)
Serious adverse events	33 (11.1)	33 (11.0)
Outcome of death[c]	6 (2.0)	4 (1.3)
Patients with any surgical complication, n (%)[d]	**175 (59.1)**	**181 (60.1)**
Maximum reported by Claven-Dindo classification grade		
1	125 (42.2)	131 (43.5)
2	32 (10.8)	25 (8.3)
≥3	18 (6.1)	25 (8.3)

DCO 10 November 2022

Abbreviations: AE, adverse events; DCO, data cut-off

[a] This includes AEs between the date of surgery (including the date of surgery) and the earliest of the date of surgery + 90 days or first dose of subsequent anti-cancer therapy; this also includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

[b] The summary of AEs possibly related to surgery and surgical complications summary reflect data collected for all patients in the modified safety analysis set who underwent surgery (including one patient assigned to the perioperative placebo arm who erroneously received a single cycle of durvalumab and was therefore included in the perioperative durvalumab arm for safety assessment), with AEs graded using the National Cancer Institute Common Toxicity Criteria for AEs, version 5.0.

[c] There were no AEs with outcome of death, possible related to surgery, within 1 day of surgery in either arm. Note: All deaths regardless of any causality within 30 days of surgery = 12 (perioperative durvalumab arm, n=4; perioperative placebo arm, n=8)

[d] Included infectious pleural effusion (perioperative placebo arm, n=1), pneumonia (perioperative durvalumab arm, n=2; perioperative placebo arm, n=1) septic shock (perioperative durvalumab arm, n=1), acute respiratory failure (perioperative placebo arm, n=1), bronchopleural fistula (perioperative durvalumab arm, n=1), interstitial lung disease (perioperative durvalumab arm, n=1), pneumonitis (perioperative durvalumab arm, n=1), pulmonary haemorrhage (perioperative placebo arm, n=1), and post-procedural pulmonary embolism (perioperative durvalumab arm, n=1).

Source: Mitsudomi et al. 2023[89]

At the D120SU (DCO [redacted]), the safety profile for neoadjuvant durvalumab + PDC followed by durvalumab monotherapy post-surgery [redacted].[21] [redacted]. A summary of AEs possibly related to a study treatment (durvalumab, PDC, or placebo) and discontinuations as the D120SU are presented in Table 27 and Table 28, respectively.[21]

Table 27. Summary of AEs possibly related to treatment or surgery at D120SU

AE category (Overall Period[a])	Number (%) of patients [b]

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	Perioperative durvalumab (N = 401)	Perioperative placebo (N = 398)
Any AE	[redacted]	[redacted]
Possibly related to any study treatment [c]	[redacted]	[redacted]
Possibly related to durvalumab/placebo [c]	[redacted]	[redacted]
Possibly related to PDC (at least one component) [c]	[redacted]	[redacted]
Possibly related to surgery [c]	[redacted]	[redacted]
Possibly related to PORT [c]	[redacted]	[redacted]
Any AE of maximum CTCAE Grade 3 or 4 [d]	[redacted]	[redacted]
Possibly related to any study treatment [c d]	[redacted]	[redacted]
Possibly related to durvalumab/placebo [c d]	[redacted]	[redacted]
Possibly related to PDC (at least one component) [c d]	[redacted]	[redacted]
Possibly related to surgery [c d]	[redacted]	[redacted]
Possibly related to PORT [c d]	[redacted]	[redacted]
Any AE with outcome of death	[redacted]	[redacted]
Possibly related to any study treatment [c]	[redacted]	[redacted]
Possibly related to durvalumab/placebo [c]	[redacted]	[redacted]
Possibly related to PDC (at least one component) [c]	[redacted]	[redacted]
Possibly related to surgery [c]	[redacted]	[redacted]
Possibly related to PORT [c]	[redacted]	[redacted]

DCO [redacted]

Study treatment includes durvalumab/placebo/SoC and excludes surgery/PORT. AEs collected between first dose and the earliest of: maximum date of (last dose or surgery) +90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; PORT, post-operative radiotherapy; SoC, standard of care

[a] Overall period refers to the neoadjuvant period, post-surgery and adjuvant period

[b] Patients with multiple events in the same category are counted only once in that category

[c] As assessed by the investigator. Missing responses are counted as possibly related. Study treatment includes durvalumab, PDC, placebo, in this context surgery is not included as a study treatment

[d] Maximum CTCAE Grade per patient/treatment period/event is considered

Source: AstraZeneca 2024[21]

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Table 28. Summary of discontinuations at D120SU

	Perioperative durvalumab (N=401)	Perioperative placebo (N=398)
Any AE leading to discontinuation of any study treatment	[redacted]	[redacted]
Leading to discontinuation of durvalumab/placebo	[redacted]	[redacted]
Possibly related to durvalumab/placebo leading to discontinuation of durvalumab/placebo [c]	[redacted]	[redacted]
Leading to discontinuation of 2 chemotherapy agents	[redacted]	[redacted]
Leading to discontinuation of PDC (at least one component), possibly related to PDC (at least one component) [c]	[redacted]	[redacted]
Any SAE (including events with outcome of death) [e]	[redacted]	[redacted]
Possibly related to any study treatment [c e]	[redacted]	[redacted]
Possibly related to durvalumab/placebo [c e]	[redacted]	[redacted]
Possibly related to PDC (at least one component) [c e]	[redacted]	[redacted]
Possibly related to surgery [c e]	[redacted]	[redacted]
Possibly related to PORT [c e]	[redacted]	[redacted]
Any imAE [f]	[redacted]	[redacted]
Infusion related reaction[g]	[redacted]	[redacted]

DCO [redacted]

Study treatment includes durvalumab/placebo/SoC and excludes Surgery/PORT. AEs collected between first dose and the earliest of: maximum date of (last dose or surgery) +90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; PDC, platinum-doublet chemotherapy; PORT, post-operative radiotherapy, imAE: immune-mediated adverse event

[a] Overall period refers to the neoadjuvant period, post-surgery and adjuvant period, ie, neoadjuvant durvalumab + PDC followed by surgery and durvalumab monotherapy, and neoadjuvant placebo + PDC followed by surgery and placebo

[b] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories

[c] As assessed by the investigator. Missing responses are counted as possibly related. Study treatment includes durvalumab, PDC, placebo, in this context surgery is not included as a study treatment

[d] Maximum CTCAE Grade per patient/treatment period/event is considered

[e] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious

[f] AEs adjudicated as imAEs

[g] Patients with AE of special interest of infusion related reaction

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Source: AstraZeneca 2024[21]

B.2.11 *Ongoing studies*

The AEGEAN study is currently ongoing and has an estimated completion date of September 2028.[77] Additional analyses for EFS are scheduled at approximately 40% (second interim analysis) and 50% (final analysis) data maturity. Disease-free survival will be tested at the second interim analysis of EFS and in the meantime, AEGEAN remains blinded. Per the MTP, OS will be tested when a significant result for DFS is reached in subsequent analyses.[20,75]

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 *Principal findings from the clinical evidence for perioperative durvalumab*

B.2.12.1.1 AEGEAN

The efficacy and safety of perioperative durvalumab for the treatment of adults with resectable NSCLC and no EGFR mutations or ALK rearrangements have been demonstrated by the AEGEAN study.

Results of the AEGEAN study to date support the positioning of durvalumab as a comprehensive perioperative treatment strategy that has the potential to address the substantial unmet need among patients who, despite undergoing curative-intent resection, still develop disease recurrence.

Perioperative durvalumab resulted in a significant improvement in pCR compared with perioperative placebo, providing an early indication of the efficacy of the perioperative durvalumab regimen. At the final analysis of pCR, an improvement in the pCR rate was observed for the perioperative durvalumab arm versus the perioperative placebo arm that was consistent with the significant improvement demonstrated at the primary analysis ($p>0.001$), with 17.2% and 4.3% achieving pCR, respectively (difference in proportions of 13.0%; 95% CI 8.7 to 17.6).[20]

Treatment with perioperative durvalumab resulted in a statistically significant, clinically meaningful, and sustained improvement in EFS corresponding to a 32% reduction in the risk of an EFS event compared with perioperative placebo (HR of 0.68 [95% CI 0.53 to 0.88; $p=0.004$]).[20] The KM plot for EFS in AEGEAN shows clear and sustained separation indicative of a survival benefit in favour of the perioperative durvalumab arm over the perioperative placebo arm.[20]

All subgroup analyses for EFS and pCR favoured the perioperative durvalumab arm.[20] Of note, EFS and pCR benefits were observed regardless of the planned neoadjuvant platinum agent.[20]

In the neoadjuvant phase of AEGEAN, treatment with durvalumab + PDC did not adversely impact the feasibility or timing of surgery in the mITT population and resulted in a numerically higher rate of R0 resections.[20] There was a similar proportion of patients in the

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perioperative durvalumab and perioperative placebo arms completing surgery (77.6% and 76.7%, respectively) and a slightly higher number of patients experienced no delays to surgery in the perioperative durvalumab arm (82.7%) than the perioperative placebo arm (77.8%).[20]

Perioperative durvalumab was well-tolerated with manageable AEs.[74] There was no increase in frequency or severity of AEs when durvalumab was used in combination with neoadjuvant PDC and the safety profile of perioperative durvalumab + neoadjuvant PDC is consistent with the known safety profiles of each agent. The most common AEs reported in the perioperative durvalumab arm were anaemia (34.0%), nausea (25.3%), and constipation (24.8%).[20] Neoadjuvant durvalumab + neoadjuvant PDC did not affect the proportion of patients with any grade AEs possibly related to surgery, or with any surgical complication.[89]

B.2.12.1.2 Evidence from ITCs

Weighting the AEGEAN population to match the CheckMate 816 population improved the relative EFS efficacy of perioperative durvalumab versus neoadjuvant PDC (+ perioperative placebo). Results of the MAICs (after weighting) showed numerical improvements with perioperative durvalumab versus neoadjuvant nivolumab + PDC, although effect sizes were associated with a degree of uncertainty; the base case analysis including all possible effect modifiers resulted in an EFS HR of [redacted] (95% CI [redacted] to [redacted]) for perioperative durvalumab versus neoadjuvant nivolumab + PDC.

Based on the preferred NMA (sensitivity analysis 2 for mITT network; random-effects model), the EFS benefit with perioperative durvalumab was nominally significant versus surgery alone (mITT) (upper 95% CrI limit less than 1) and for the other comparisons, the estimated EFS HR was in favour of perioperative durvalumab, but with 95% CrIs for HR including 1. Of note, in the fixed-effect model, the EFS benefit with perioperative durvalumab was nominally significant versus neoadjuvant PDC, adjuvant PDC and surgery alone (mITT) (upper 95% CrI limit less than 1).

B.2.12.2 *Strengths of the evidence base*

AEGEAN is the first phase 3 trial to describe the benefit of perioperative immunotherapy with neoadjuvant chemotherapy in NSCLC. Immuno-oncology therapy trials in NSCLC to date have demonstrated reduced recurrence and improved survival in respective neoadjuvant and adjuvant settings only.[57,66,67] The perioperative regimen used in AEGEAN demonstrates that the two actions of priming the patient's immune system in the neoadjuvant setting (while the primary tumour and lymph nodes are present) and preventing the growth and spread of micrometastases in the neoadjuvant as well as the adjuvant setting (the time period where the risk of recurrence is the highest) is advantageous and has the potential to improve long-term outcomes such as survival.[9,10,17-19]

AEGEAN is a randomised, placebo-controlled, double-blind, multicentre trial, and is therefore robustly designed to assess the safety and efficacy of durvalumab in the perioperative setting.[20] The baseline patient and disease characteristics of the mITT population were well-balanced between the perioperative durvalumab and placebo treatment arms.[20]

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The AEGEAN study population is generalisable to patients with resectable NSCLC in the UK. AEGEAN includes more than 700 participants from multiple countries with approximately 40% of participants enrolled in Europe, 40% in Asia, 10% in North America, and 10% in South America.[20] On average, participants in AEGEAN are slightly younger than patients with lung cancer in the UK (median age was 65 years in AEGEAN and 74 years in UK clinical practice).[20,29] To be eligible for inclusion in AEGEAN, participants had to have a good performance status (Eastern Cooperative Group Performance status (ECOG PS) of 0 or 1).[20] In UK clinical practice, patients with lung cancer have ECOG PS scores that range from 0 to 4.[29] These differences in age and ECOG PS between AEGEAN and UK clinical practice are observed in most clinical trials for cancer treatments and are not expected to impact the interpretation of the efficacy and safety results of AEGEAN. This was confirmed by clinical experts who agreed that the AEGEAN study population was entirely generalisable to patients seen in UK clinical practice. The generalisability of AEGEAN is similar to that of CheckMate 816. Clinical experts stated that patients presenting for surgery in the UK are PD-L1-positive.[22]

The study evaluated EFS as a primary endpoint along with pCR. Event-free survival considers the occurrence of multiple patient-relevant events, is not confounded by subsequent therapy following progression or recurrence, and is considered a potential surrogate for OS.[80] Since EFS includes progression events precluding surgery, recurrence events after surgery, and death, it is aligned with the treatment goals of this setting and provides a direct measure of treatment efficacy across both neoadjuvant and adjuvant treatment periods with surgery as a curative intent therapeutic strategy. An improvement in EFS may reduce clinical and economic burden by keeping patients in a recurrence-free state.[10,14,15,45]

The ITCs have several strengths. The evidence base informing the ITCs was identified via a comprehensive and recent SLR and the resulting analyses produced estimates of comparative effectiveness for perioperative durvalumab versus a range of comparators that are used in UK clinical practice for the treatment of resectable NSCLC. Further, all ITC methods were in accordance with NICE DSU TSD 18[90] and the MAIC base case considered all possible effect modifiers.[103] In addition to the conventional ITC analysis, piecewise ITCs with time intervals of 0-to-3-months and 3+ months were also conducted to account for the delayed separation of EFS curves in AEGEAN and CheckMate 816. Few events had occurred in 0-to-3-month time interval across trials, limiting the robustness of the piecewise ITCs for this time interval. As a simplifying assumption, it was considered reasonable to assume that there would be no/limited difference in EFS between any of the regimens (including between immunotherapy-based regimens) during this time interval, in the absence of any clear separation between the KM curves within the respective trials.

The NMAs were conducted to make full use of the evidence available from multiple trials for surgery alone and adjuvant PDC (versus a common comparator of neoadjuvant PDC).

B.2.12.3 *Potential limitations*

AEGEAN is evaluating a new treatment regimen in resectable NSCLC. The current pathway of care in the UK does not include a perioperative treatment regimen and treatment options for patients include neoadjuvant nivolumab + PDC, adjuvant PDC, or surgery alone.[3]

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In AEGEAN, perioperative durvalumab + neoadjuvant PDC is compared against a perioperative placebo + neoadjuvant PDC.[20] Neoadjuvant chemotherapy alone is not recommended by NICE for patients with stage I and II, resectable NSCLC, the standard of care for most patients is surgery (with the recent addition of neoadjuvant nivolumab to the treatment pathway), although some patients may still be offered neoadjuvant chemotherapy prior to surgery in UK clinical practice.[3,50] Thus, the treatment received by the control arm of AEGEAN may not represent the treatment currently received by the majority of patients in UK clinical practice. Despite not being fully representative of UK clinical practice, the control arm in AEGEAN allows for comparison with neoadjuvant nivolumab + PDC via ITC using the common comparator of neoadjuvant PDC.

At the time of AEGEAN study design, neoadjuvant nivolumab + PDC was not available. It was only recently recommended in 2023 by NICE.[50] The CheckMate 816 trial for neoadjuvant nivolumab + PDC also used neoadjuvant PDC as a control arm[50,66] In the absence of direct comparative data for perioperative durvalumab versus neoadjuvant nivolumab + PDC, adjuvant PDC, or surgery alone ITCs have been performed, the methods for which are described in Appendix D.2 and the results of which are presented in Section B.2.9.

For the ITCs, a thorough inspection of subgroup analyses and stratification factors was performed to identify potential effect modifiers, and for the MAIC versus neoadjuvant nivolumab + PDC, all identified effect modifiers were adjusted for, but there could still be unmeasured differences not accounted for. In addition, weighting to match CheckMate 816 reduces the ESS, thus reduces the precision of the estimates. Weighting also produces estimates of relative efficacy in the comparator trial population. However, the results of the analyses are still considered generalisable to the population that might use the perioperative durvalumab regimen in UK clinical practice (e.g., across stage and PD-L1; cisplatin-treated patients).

To conduct anchored comparisons, other assumptions associated with ITC (and not unique to MAICs) were required e.g., there were differences between the AEGEAN and CheckMate 816 trials in the common comparator for the number of neoadjuvant chemotherapy cycles, permitted adjuvant chemotherapy, and documented exclusion of EGFR/ALK positive tumours which could not be accounted for in the MAIC. In the case of differences between trials in the treatment characteristics of the common comparator, these are not expected to have considerable impact on EFS outcomes.[64]

The NMAs were conducted on sparse networks, with only one study, NATCH, providing estimates for adjuvant PDC versus neoadjuvant PDC. Heterogeneity between studies was identified in potential effect modifiers (e.g., stage, type of chemotherapy, region); therefore, sensitivity analyses were explored, and the random-effects model was preferred.

The results of AEGEAN presented in this submission and used in the ITCs are from early planned analyses. AEGEAN is ongoing and will provide further evidence for longer-term EFS, as well as DFS and OS at future planned analyses. The first interim analysis of EFS was planned to occur at approximately 30% data maturity.[20] This first interim analysis actually occurred at a median follow-up time in censored patients of 11.7 months and 31.9% data maturity for EFS, and for an early analysis, resulted in a statistically significant EFS

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result in favour of perioperative durvalumab versus perioperative placebo.[20] At the interim analysis of EFS, around [redacted]% of patients in both treatment arms remained on adjuvant treatment. As described in Section 0, DFS and OS will be tested in future planned analyses of AEGEAN.[20,75]

B.2.12.4 *Conclusions on the clinical effectiveness of perioperative durvalumab*

Surgery with curative intent is the mainstay treatment for eligible patients with resectable NSCLC.[3] Despite the curative intent, however, disease recurrence after surgery can occur rapidly and recurrence rates for patients with stage II-III NSCLC are high.[8,11] Furthermore, the risk of recurrence is highest in the first year post-resection (peaking around 12 months post-surgery).[9,10] Patients with stage II-III NSCLC that develop recurrent disease post-resection have poor long-term outcomes[8,10,12] and there is a substantial unmet need for treatments that reduce recurrence and improve survival after complete resection of NSCLC.

To date, immuno-oncology therapies have demonstrated reduced recurrence and improved survival benefits for patients with resectable NSCLC in respective neoadjuvant and adjuvant settings only.[57,66,67] A perioperative regimen can offer a more comprehensive treatment approach when the risk of recurrence is the highest.[9,10,17-19] The use of immuno-oncology therapy in the neoadjuvant setting has the advantage of priming the patient's immune system whilst the tumour and any involved lymph nodes are still present prior to surgery.[17] Following resection, continuation of immuno-oncology therapy in the adjuvant setting (as per the perioperative approach) may be beneficial, to consolidate the immune response and suppress/eradicate micrometastases, and thus potentially delay or prevent disease recurrence.[19] A perioperative immuno-oncology therapy regimen may therefore further improve long-term outcomes and provide the possibility of cure.

The findings of AEGEAN demonstrate that treatment with perioperative durvalumab results in statistically significant and clinically meaningful improvements in EFS compared with perioperative placebo for patients with resectable NSCLC (p=0.004).[74] EFS is considered a surrogate outcome for OS in resectable NSCLC.[83-85] The KM curves for EFS in AEGEAN are similar to 3 months, the time point at which the first RECIST scan occurred post randomisation at the completion of the neoadjuvant phase, but then showed clear and sustained separation indicative of a survival benefit in favour of perioperative durvalumab over perioperative placebo. Further, the D120SU (DCO [redacted]) showed [redacted].[21] The subsequent DCO supports [redacted].

Overall, the results of the ITCs support the use of the perioperative durvalumab regimen, as investigated in AEGEAN, as a new treatment option for patients with resectable NSCLC in the UK. This is based on improvements in EFS versus the neoadjuvant nivolumab + PDC estimated by the MAIC and versus adjuvant PDC and surgery alone estimated by NMAs.

Importantly, the addition of perioperative durvalumab to neoadjuvant PDC in AEGEAN did not adversely impact the feasibility or timing of surgery and resulted in a numerically higher

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rate of R0 resections.[20] On this basis, the use of perioperative durvalumab in UK clinical practice is not expected to impact surgical outcomes for patients.

The statistically significant and promising EFS result in favour of perioperative durvalumab versus perioperative placebo was obtained at an early analysis.[20] As AEGEAN is ongoing, it will provide further evidence for longer-term EFS, as well as DFS and OS, at future planned analyses.

The AEGEAN trial results, taken together with the favourable results of the ITCs versus UK standard of care comparators, suggest that perioperative durvalumab meets the substantial need for a treatment that lowers the risk of recurrence or death and therefore improves the possibility of successful long-term outcomes, including 'cure', for patients with resectable NSCLC in the UK.

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B.3. Cost effectiveness

- **A four-state semi-Markov model was implemented to analyse the cost-effectiveness of durvalumab with platinum-doublet chemotherapy (PDC) as neoadjuvant treatment followed by durvalumab monotherapy as adjuvant treatment (perioperative durvalumab) for patients with resectable NSCLC to current SoC in the UK versus:**
    - Neoadjuvant PDC
    - Neoadjuvant nivolumab with PDC
    - Surgery alone (i.e., active monitoring), and
    - Adjuvant PDC
- **The four health states were event-free (EF), locoregional recurrence (LRR), distant metastases (DM), and death**
- **The population and key clinical inputs for perioperative durvalumab and neoadjuvant PDC were modelled based on the AEGEAN trial and the efficacy of outside trial comparators (i.e., neoadjuvant PDC, neoadjuvant nivolumab + PDC, surgery alone and adjuvant PDC) was informed by an ITC using data identified in an SLR**
- **Costs in the model included treatment acquisition and administration, surgical procedures, AEs, health care resource use (e.g., tests, scans, visits to medical specialists) and end-of-life care**
- **Health state utility values were based on AEGEAN and other relevant clinical trials, and the model accounts for disutilities related to grade 3 and 4 AEs**
- **In the deterministic analyses, the results of the cost-effectiveness analysis indicated that perioperative durvalumab led to improved EFS versus all comparators that resulted in a mean incremental cost-effectiveness ratio (ICER) of £4,708, £19,575 and £4,458 for perioperative durvalumab versus neoadjuvant PDC, neoadjuvant nivolumab + PDC, and adjuvant PDC, respectively; perioperative durvalumab dominated surgery alone**
- **Probabilistic analyses were consistent with the probabilistic analyses, with a corresponding cost per QALY of £6,194, £23,625 and £4,872 for perioperative durvalumab versus neoadjuvant PDC, neoadjuvant nivolumab + PDC, and adjuvant PDC, respectively; perioperative durvalumab dominated surgery alone**
- **The outcomes of scenario analyses, where alternative model assumptions were assessed, aligned with the results observed in the base case**

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B.3.1 *Published cost-effectiveness studies*

B.3.1.1 *Identification of studies*

SLRs were conducted to identify published economic evaluations of interventions for patients with NSCLC, including evidence relating to the HRQoL and utility (humanistic burden), and cost/resource use (economic burden) that may be of relevance to this submission. Full details of all SLRs (including identified HRQoL and cost/resource studies) are presented in Appendix G, respectively.

Furthermore, previous health technology assessment (HTA) submissions were reviewed to compare model structures in cost-effectiveness analyses across neoadjuvant and adjuvant oncology treatments to understand the appropriate model structure for the analysis of perioperative durvalumab in resectable NSCLC. A review of NICE and Canadian Agency for Drugs and Technologies in Health (CADTH) was initially conducted between August to September 2022, and was updated in March 2023. A total of 13 and 12 appraisals for NICE and CADTH, respectively, were identified.

No economic evaluations were identified for durvalumab in this indication.

B.3.1.2 *Description of identified studies*

Table 29 provides an overview of the cost-effectiveness models in neoadjuvant and adjuvant oncology settings appraised by NICE, respectively. Details on the CADTH appraisals are provided in Appendix G.

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Table 29. Summary of NICE TAs

TA, year	Disease setting	Intervention	Comparators	Model type	Model accepted by NICE	Reimbursement decision
TA761, 2022[59]	NSCLC Adjuvant	Osimertinib	Established clinical management without osimertinib (active monitoring)	Semi-Markov (5) 1) DFS 2) LRR 3) DM 1 4) DM 2 5) Death	Yes	Recommended for use within the CDF
TA823, 2022[23]	NSCLC Adjuvant	Atezolizumab	Established clinical management without osimertinib (active monitoring)	Markov (5) 1) DFS 2) LRR (curative or palliative/no treatment) 3) DM 1 (on/off treatment) 4) DM 2 (on/off treatment) 5) Death	Initial model: No Updated model: Yes	Recommended for use within the CDF
TA876, 2023[50]	NSCLC Neoadjuvant	Nivolumab	Neoadjuvant chemoradiotherapy, surgery alone (SoC), adjuvant chemotherapy	Semi-Markov (4) 1) EFS 2) LRR 3) DM 4) Death	Yes	Recommended
TA424, 2016[104]	Breast Cancer Neoadjuvant	Pertuzumab	Standard neoadjuvant therapy without pertuzumab: pertuzumab, trastuzumab and docetaxel, compared with trastuzumab and docetaxel	Markov (6) 1) EFS 2) LRR 3) Remission 4) Metastatic not progressed 5) Metastatic progressed 6) Death	Yes	Recommended

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TA, year	Disease setting	Intervention	Comparators	Model type	Model accepted by NICE	Reimbursement decision
TA632, 2020[105]	Breast Cancer Adjuvant	Trastuzumab emtansine	Standard adjuvant therapies including trastuzumab. For people with node-positive disease, pertuzumab in combination with	Markov (7) 1) iDFS on treatment 2) iDFS off treatment 3) Non-metastatic recurrence 4) Remission 5) 1L metastatic breast cancer	Yes	Recommended
TA569, 2019[106]	Breast Cancer Adjuvant	Pertuzumab	Standard adjuvant therapy without pertuzumab for HER2-positive breast cancer: trastuzumab in combination with chemotherapy	Markov (7) 1) iDFS – on treatment 2) iDFS – off treatment 3) Non-metastatic recurrence 4) Remission 5) 1L metastatic breast cancer 6) 2L+ metastatic breast cancer 7) Death	Yes	Recommended
TA612, 2019[107]	Breast Cancer Adjuvant	Neratinib	Standard treatment with no further HER2-directed therapy Standard treatment is defined as placebo in the ExteNET trial.	Markov (5) 1) iDFS 2) LRR 3) Remission 4) DR 5) Death	Yes	Recommended
TA851, 2022[108]	Breast Cancer Perioperative	Pembrolizumab	Neoadjuvant: carboplatin + paclitaxel followed by doxorubicin/ epirubicin + cyclophosphamide Adjuvant: placebo	Markov (4) 1) EFS 2) LRR 3) DM 4) Death	Yes	Recommended

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TA, year	Disease setting	Intervention	Comparators	Model type	Model accepted by NICE	Reimbursement decision
TA746, 2021[109]	GIST Adjuvant	Nivolumab	Routine surveillance	Semi-Markov (3) 1) Disease free 2) Recurred disease 3) Death	Yes	Recommended
TA326, 2014[110]	GIST Adjuvant	Imatinib	No adjuvant treatment	Markov (4) 1) Remain recurrence free 2) Recurrent GIST (1st or 2nd recurrence) 3) Progressive disease 4) Death (GIST or other)	Yes	Recommended
TA544, 2018[111]	Melanoma Adjuvant	Dabrafenib	Routine surveillance	Markov (4) 1) RFS 2) LRR 3) DR 4) Death	Yes	Recommended
TA766, 2022[112]	Melanoma Adjuvant	Pembrolizumab	Routine surveillance	Markov (4) 1) RF 2) LRR 3) DM 4) Death	Yes	Recommended
TA684, 2021[113]	Melanoma Adjuvant	Nivolumab	Routine surveillance; ipilimumab	Markov and PSM (3) Start: post resection 1) RF 2) Post recurrence 4) Death	Markov: No PSM: Yes	Recommended

* The company's original economic modelling approach was not appropriate for decision-making; the updated approach was considered appropriate.
** Due to uncertainty regarding the modelling of OS, the committee considered the PSM but not the Markov model.

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Abbreviations: 1L, first line; 2L, second line; CDF, Cancer Drug Fund; DFS, disease-free survival; DM, distant metastasis; DR, distant recurrence; EFS, event-free survival, ERG, evidence review group; GIST, gastrointestinal cancer; HER2, human epidermal growth factor receptor 2; ID, identification; iDFS, invasive disease-free survival; LRR, locoregional recurrence; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PSM, partitioned survival model; RF, recurrence free; RFS, relapse-free survival; SoC, standard of care; TA, technology appraisal

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B.3.1.3 *Quality assessment of identified studies*

A quality assessment of identified studies was not conducted.

B.3.2 *Economic analysis*

From a search of previous cost-effectiveness studies, no submissions assessed perioperative treatments in early NSCLC. The only relevant economic evaluation focused on appraising neoadjuvant nivolumab in early NSCLC (PC0303, TA876).[50,114] As such, a similar model structure (i.e., semi-Markov model with four health states) was developed. However, the data used to inform the transition probabilities between health states differs. Therefore, a de novo economic model in Microsoft Excel® was built to address the decision problem. The key characteristics of the model are shown in Table 30.

Table 30. Characteristics of de novo economic model

Aspect	Details	Justification
Model structure	A semi-Markov state transition model, with four health states: event-free, locoregional recurrence, distant metastatic, and Death	The approach is in line with the clinical pathway for the patient population and consistent with previous NICE technology appraisals in early-stage cancer (e.g.,TA876)[50].The model structure was validated by UK clinical experts in an advisory board[22]
Patient population	Stage IIA-IIB resectable NSCLC with no known EGFR mutations or ALK aberrations	Aligned with anticipated label for perioperative durvalumab and as per NICE scope[115]
Intervention	Perioperative durvalumab	As per NICE scope[115]
Comparator	Neoadjuvant PDC Neoadjuvant nivolumab + PDC Surgery alone Adjuvant PDC	As per NICE scope[115] and AEGEAN
Perspective	UK NHS and PSS	In line with the NICE reference case[116]
Time horizon	Lifetime (36 years)	To align with the NICE reference case[116] for the patient population (<1% of the patients in the perioperative durvalumab arm remain alive at 36 years in the analysis)
Cycle length	1 month (4.35 weeks)	To align with recurrent costs and timing of patients' treatment, and sufficiently granular to capture events occurring during disease progression
Half-cycle correction	Applied in the base case analysis	To adjust for timing of state transitions throughout the cycle
Discounting	3.5% for costs and benefits	In line with the NICE reference case[116]

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Aspect	Details	Justification
Clinical effectiveness – EF	AEGEAN	Overall population of AEGEAN aligns with the considered population in the model
Site of recurrence	[redacted] locoregional recurrence, [redacted] distant metastases	Validated by UK clinical experts.[22]
Clinical effectiveness – LRR	Clinical effectiveness: PROCLAIM trial,[117] PACIFIC trial,[118] literature (Wong et al. 2016[12]) Treatment market shares: literature, AEGEAN and ADAURA trials	• Due to limited post-recurrence follow-up data available from AEGEAN at the data cut-off (November 2022), data from the PROCLAIM trial,[117] PACIFIC trial[118] and literature were used.[12] • For the treatment market shares, literature and assumptions based on the AEGEAN and ADAURA trials were used, Market shares were also validated by UK clinical experts.[22]
Clinical effectiveness – DM	Clinical effectiveness: literature Treatment market shares: literature and AEGEAN trial	• Due to limited post-recurrence follow-up data available from AEGEAN (from the first interim analysis), data on PFS and OS from the pivotal trials of SoC (pembrolizumab ± chemotherapy or platinum-based chemotherapy for those not eligible for IO therapy) for first-line, EGFRwt/ALK-, metastatic NSCLC: KEYNOTE-024 (PD-L1 ≥50%),[119] KEYNOTE-189 (non-squamous)[120] and KEYNOTE-407 (squamous)[121] and BSC (Wong et al. 2016[12]) were used. • For the treatment market shares, literature and assumptions based on the AEGEAN trial were used. Market shares were also validated by UK clinical experts.[22]
Treatment and healthcare resource use costs	NHS reference costs; BNF; eMIT; PSSRU; published literature, resource utilisation and costs accepted in previous NICE submissions	Widely used and accepted sources of cost and resource use data in UK HTAs
Health-related quality of life	AEGEAN trial (AEGEAN EQ-5D-5L mapped via the Hernandez Alava DSU algorithm to UK EQ-5D-3L value set)[122] and literature	HRQoL was assessed in the AEGEAN trial using the EQ-5D-5L questionnaire. Given that HRQoL data was not available from the AEGEAN trial to inform the DM health state, data from a previously accepted NICE submission, based on KEYNOTE-189 trial was used[123]

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Aspect	Details	Justification
Adverse event rates and costs	EF only: AEGEAN trial (Grade 3-4 with incidence ≥ 5% in any treatment arm) for AEGEAN therapies and literature (for non-AEGEAN therapies)	The inclusion of adverse events experienced during neoadjuvant/ adjuvant treatment period only, as well as the criteria for AE grade and incidence are in line with previous submissions in the same therapeutic area (TA761, TA823, TA876)[23,50,59]
Assumption of cure	The model assumes that 95% of patients are cured if remaining in EF after 5 years	To reflect the expected clinical outcomes using the AEGEAN trial data (from the first interim analysis), a 5-year cure timepoint was applied, taking into account the expectation of a plateau towards the 5-year mark: event-free patients are typically discharged and not followed by clinicians after 5 years, and therefore are considered to be functionally cured. This assumption is consistent with the preferred approach described in NICE technology appraisals in adjuvant, early-stage cancer (TA569, TA642).[106,124] Different cure timepoints were tested in scenario analyses. This assumption was also validated by UK clinical experts.[22]
IO retreatment	In post-recurrence, i.e., LRR and DM health states, retreatment with IO is expected for patients who have received IO as adjuvant or neoadjuvant therapy in the resectable setting and have not progressed/ experienced recurrence within 6 months since completing previous IO treatment	This assumption is in line with clinical feedback that was received in previous HTA submissions in early-stage NSCLC (TA823 and TA876).[23,50] Different timepoints for permitting IO retreatment, as well as no IO retreatment were tested in scenario analyses. This assumption was also validated by UK clinical experts.[22]

Abbreviations: BNF, British National Formulary; BSC, Best Supportive Care; DM, distant metastasis; EF, event-free; eMIT, electronic market information tool; IO, immuno-oncology; NICE, National Institute for Health and Care Excellence; NSCLC, non-small-cell lung cancer; PSS, Personal Social Services.

B.3.2.1 *Patient population*

The base-case model patient population is aligned with the anticipated indication for perioperative durvalumab and is defined as adults with resectable NSCLC (stages IIA to IIIB [N2 only], according to AJCC staging 8th edition) whose tumours have no EGFR mutations (EGFRm) or ALK aberrations (i.e., the mITT population included in the primary analysis of the AEGEAN trial). Patient characteristics for the model were validated by clinical experts to be relevant for England.[22] Table 11, presented in Section B.2.3.3, provides an overview of certain baseline characteristic such as age, sex, region, and disease stage.

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

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B.3.2.2 *Model structure*

A semi-Markov model was developed in Microsoft Excel®, comprising four mutually exclusive health states that represent the disease course and survival for a cohort of patients that present with resectable early stage IIA/IIIB NSCLC. The model structure was selected based on the following reasons.

- A semi-Markov (state transition) model is a useful tool to simulate long-term efficacy outcomes when OS data are not yet available or are relatively immature, such as in the case of AEGEAN and other trials in resectable NSCLC. In a Markov state transition model, transition probabilities are used to determine the probability that a patient experiences a certain event or outcome in each model cycle. This is then used to model the flow of patients between (or within) health states over time. Model predictions of OS are therefore dependent on the mortality rates for each health state and the number at risk in each state over time, which is determined by the rates of progression from earlier health states. Therefore, there is a structural link between mortality and earlier progression events. Transitions from subsequent health states can be determined from external sources of evidence and thus are not reliant on extrapolation of immature OS data (as would be the case when using a partitioned survival analysis).
- The use of a semi-Markov model can improve transparency around the mechanisms and processes underpinning the results generated using extrapolation techniques, as well as facilitate meaningful sensitivity analyses.
- The structure is consistent with approaches adopted in the majority of economic evaluations submitted to HTA bodies in the neoadjuvant, adjuvant and perioperative settings (outlined in Table 29).
- According to the NICE guidelines manual, the use of Markov model may be deemed appropriate in cases where the cost effectiveness analysis requires a complex disease pathway to be analysed.[125]

The four health states in the economic model are “event-free” (EF), “locoregional recurrence” (LRR), “distant metastases” (DM), and “death” as an absorbing state. The model structure assumes that patients who progress to LRR or DM cannot subsequently move back to a previous health state. That is, patients in the model remain in the current health state until further disease progression or death. Figure 20 presents the model’s structure and its four health states.

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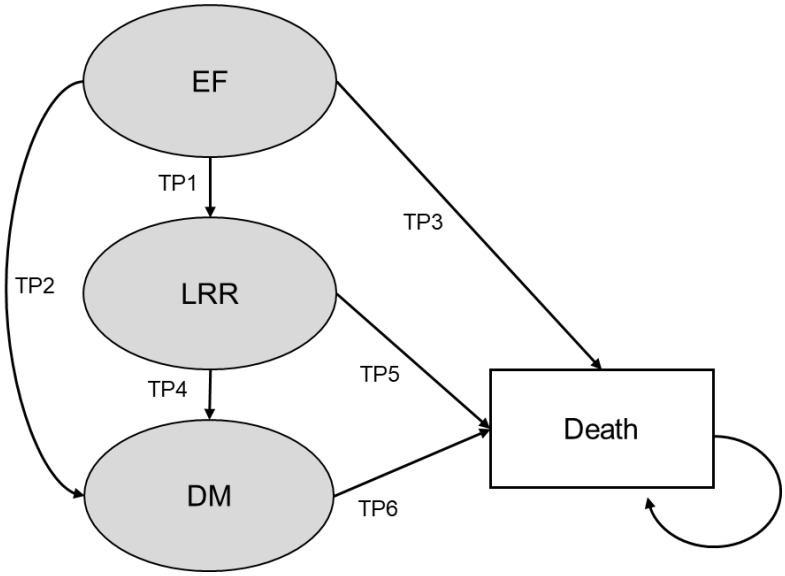
Figure 20. Economic model structure



Abbreviations: EF, event-free; DM, distant metastasis; LRR, locoregional recurrence; TP, transition probability.

The model was developed from a UK healthcare perspective, following NICE guidelines. A time horizon of 36 years (i.e., lifetime horizon) was used to predict all relevant costs and health effects throughout a patients' journey. A one-month (i.e., 4.35 weeks) cycle length was employed, and half-cycle correction was utilised to mitigate potential bias from events that could occur at different points throughout the model cycle. The model discounted the costs and health benefits on a yearly basis at a rate of 3.5% per annum, per NICE recommendations.[116]

Patients enter the model in the EF health state. Transition probabilities (TPs) were used to model the flow of patients between (or within) health states over time. From the EF state, patients can progress to either LRR (TP1), to DM (TP2), or to death (TP3). Patients transition to LRR from EF if they experience locoregional recurrence and can either receive active treatment or no treatment (i.e., best supportive care (BSC)). Patients receiving active treatment in LRR who then develop metastases or die transition to the DM (TP4) or death (TP5) state, respectively. Those receiving no treatment (BSC) can only progress to the death state directly (TP5). Patients who develop metastases and move to the DM state from either EF (TP2) or LRR (TP4), can only move to the death state (TP6) from this point onwards (see Figure 20).

B.3.2.3 *Intervention technology and comparators*

Durvalumab is administered IV at a dose of 1500mg in combination with PDC Q3W for a maximum of four cycles (neoadjuvant period) followed by durvalumab 1500 mg IV Q4W for a maximum of 12 cycles (adjuvant period).

The comparators list includes SoC treatment options in England and Wales, i.e., neoadjuvant PDC, neoadjuvant nivolumab with PDC, surgery alone and adjuvant PDC. The current pathway of care, including proposed place of perioperative durvalumab in resectable NSCLC has been previously presented in Figure 2.

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B.3.3 *Clinical parameters and variables*

The AEGEAN trial, a phase III RCT evaluating neoadjuvant durvalumab in combination with PDC followed by adjuvant durvalumab monotherapy vs. neoadjuvant placebo plus PDC followed by adjuvant placebo was the primary source of clinical data for the economic model. The data sources that were used for each transition between health states are summarised in Table 31.

AEGEAN provided efficacy, time on treatment, safety, and HRQoL inputs for the economic model. Specifically, AEGEAN EFS data were used to estimate transition probabilities from EF to LRR, EF to DM and EF to Death. Given the duration of follow-up in the AEGEAN trial at the time of the EFS IA1, and that RECIST tumour assessments were only scheduled in the AEGEAN trial up to the first recurrence (or withdrawal of consent, or death), other sources of efficacy were required to model transitions from the post-recurrence health states (LRR and DM). Data from the literature were therefore used for the remaining transition probabilities (i.e., LRR to DM, LRR to Death, and DM to Death), outlined in Table 31. These were primarily based on the pivotal trials and primary sources of evidence used in NICE technology appraisals of IO therapies used in later stages of NSCLC (i.e., PACIFIC in TA798 [for LRR]; KEYNOTE-024, KEYNOTE-189 and KEYNOTE-407 in TA531, TA683 and TA770, respectively [for DM]).[123,126-128]

Table 31. Overview of the clinical inputs

Transition	Base-case source
TP1: EF → LRR	Analysis of AEGEAN data (from EFS and proportion of RECIST recurrence events that were local)[75]
TP2: EF → DM	Analysis of AEGEAN data (from EFS and proportion of RECIST recurrence events that were not local)[75]
TP3: EF → Death	Analysis of AEGEAN data (from EFS; time to death as first EFS event)[75]
TP4: LRR → DM [a]	Based on PACIFIC trial (TTP), as used in TA798[118,127]
TP5: LRR → Death [a]	Based on PACIFIC trial (difference in PFS and TTP), as used in TA798[118,127]
TP6: DM → Death	Based on KEYNOTE trials for pembrolizumab (with or without chemotherapy) (PFS and OS) across relevant populations (KEYNOTE-024, KEYNOTE-189 and KEYNOTE-407),[36,119-121] as used in TA531, TA683 and TA770.[123,126,128] PFS and OS included in nested partitioned survival model approach

[a] Additional sources of efficacy were used to model time from entry in to LRR to PACIFIC randomisation, which occurred after CRT (PROCLAIM),[117] and for patients receiving BSC (Wong et al. 2016)[12]
Abbreviations: EF, event-free; DM, distant metastasis; GPM, general population mortality; HR, hazard ratio; LRR, locoregional recurrence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PrePS, pre-progression survival; RWE, real-world evidence; SoC, standard of care; TP, transition probability; TTP, time to progression.

B.3.3.1 *Modelling event-free health state*

Transition probabilities originating from the EF state were calculated through survival analyses of individual patient-level data from the AEGEAN trial. EFS was used to obtain transition probabilities for three key components: EF to LRR, EF to DM, and EF to death.

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Due to a low number of events recorded in the AEGEAN trial for EF to LRR and EF to DM, extrapolation from the available data could result in a high degree of uncertainty. Therefore, transition probabilities for each individual transition were derived based on the extrapolated EFS data, along with the proportion of patients experiencing either LRR or DM. Other NICE technology appraisals (e.g., TA823 and TA851) adopted a comparable approach in assessing neoadjuvant and adjuvant therapies within oncology.[23,108]

Similarly, while the number of death events as a first EFS event (to calculate EF to death) were low within each treatment arm, pooling the data across arms enabled more robust extrapolation. The transition probabilities for EF to death were derived from these extrapolations based on death as the first EFS event. Despite the low number of events, extrapolation of death as a first EFS event was considered necessary in order to capture changes in the risk of death (pre-recurrence) over time (e.g., due to increasing age). To ensure that the extrapolated data did not produce clinically implausible outcomes, the transition probabilities for EF to death were constrained to be the same as general population mortality, at a minimum. More details on the transition probabilities from EF to death are presented below, in Section B.3.3.3.2.

B.3.3.1.1 Parametric extrapolation methods

At the time of the first AEGEAN interim analysis (DCO 10 November 2022), EFS maturity was 31.9%, with median follow-up for EFS of 11.7 months (range: 0 to 46.1) in censored patients.[20] In line with NICE DSU TSD 14,[129] it was necessary to assess the cost effectiveness of perioperative durvalumab over a lifetime horizon. Therefore, parametric survival analysis was undertaken to extrapolate EFS.

In accordance with standard practice and guidance from the NICE DSU, the extrapolation of the survival data was conducted using a range of standard parametric survival models including exponential, Weibull, Gompertz, lognormal, loglogistic, and generalised gamma.[129]

The analytical process involved testing the various statistical distributions and assessing their fits over the observed trial period. The best-fitting distributions were selected in line with NICE DSU guidance on the analysis of survival outcomes for economic evaluations, alongside clinical trials.[129] This involved the assessment of both statistical goodness of fit as well as the clinical plausibility of the extrapolated outcomes. Thus, while the process involves distinct steps, it is not necessarily algorithmic.

- **Hazard plots**: log-cumulative hazard plots, smoothed hazards plots and Schoenfeld residuals were used to assess the proportional hazards assumption (PHA) and the appropriateness of certain parametric distributions and modelling approaches. A visual inspection of the plots were also used to assess whether use of jointly or individually fitted survival models were more appropriate.
    - Log-cumulative hazard plots consider the observed hazard rates over time, which is important when considering suitable parametric models since different models incorporate different hazard functions. For example, exponential models are only appropriate if the observed hazard is approximately constant and non-zero. Weibull and Gompertz models incorporate monotonic hazards, whilst loglogistic

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and lognormal models can incorporate non-monotonic hazards but typically have long tails due to reducing hazards over time after a certain point. This plot can also assess whether the PHA between two treatment groups is reasonable, indicated by parallel curves.

  - The Schoenfeld residuals is a quantitative approach to evaluate the PHA. The Schoenfeld residuals graph plots time on the x-axis versus the Schoenfeld residuals on the y-axis, whilst the log hazard plots time on the x-axis vs the log(Survival) on the y-axis. The PHA can be assumed to hold if the plot of the residuals against time shows a linear trend with slope=0 and/or the log hazard plot shows a linear trend between treatment arms.

  - The smoothed hazards plots are also a useful way of assessing the hazard rates from the KM over time, so that an appropriate parametric distribution which is in line with the smoothed hazards can be used.

- **Statistical goodness of fit**: The Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) provide a measure of goodness of fit for each of the parametric distributions obtained. For each distribution, the AIC and BIC values were compared and used to help determine the best fits to the observed data (note that this only provides an estimation of the goodness of fits over the observed trial period, and not the extrapolation period).

- **Visual inspection**: The goodness of fit of the parametric curves to the KM data from the AEGEAN trial was visually assessed to ensure that the predictions aligned with the trial data.

- **Clinical plausibility and external validation**: To ensure realistic predictions beyond the trial period, clinical judgment of plausibility of extrapolations is required. UK clinical expert opinion was sought in a UK advisory board to understand outcomes that could be expected under the current SoC, and to validate the survival extrapolations for neoadjuvant PDC. External evidence was also considered and used where appropriate to validate the model extrapolations.[22,64]

The model selection for EFS follows the model selection process algorithm shown in Figure 21.

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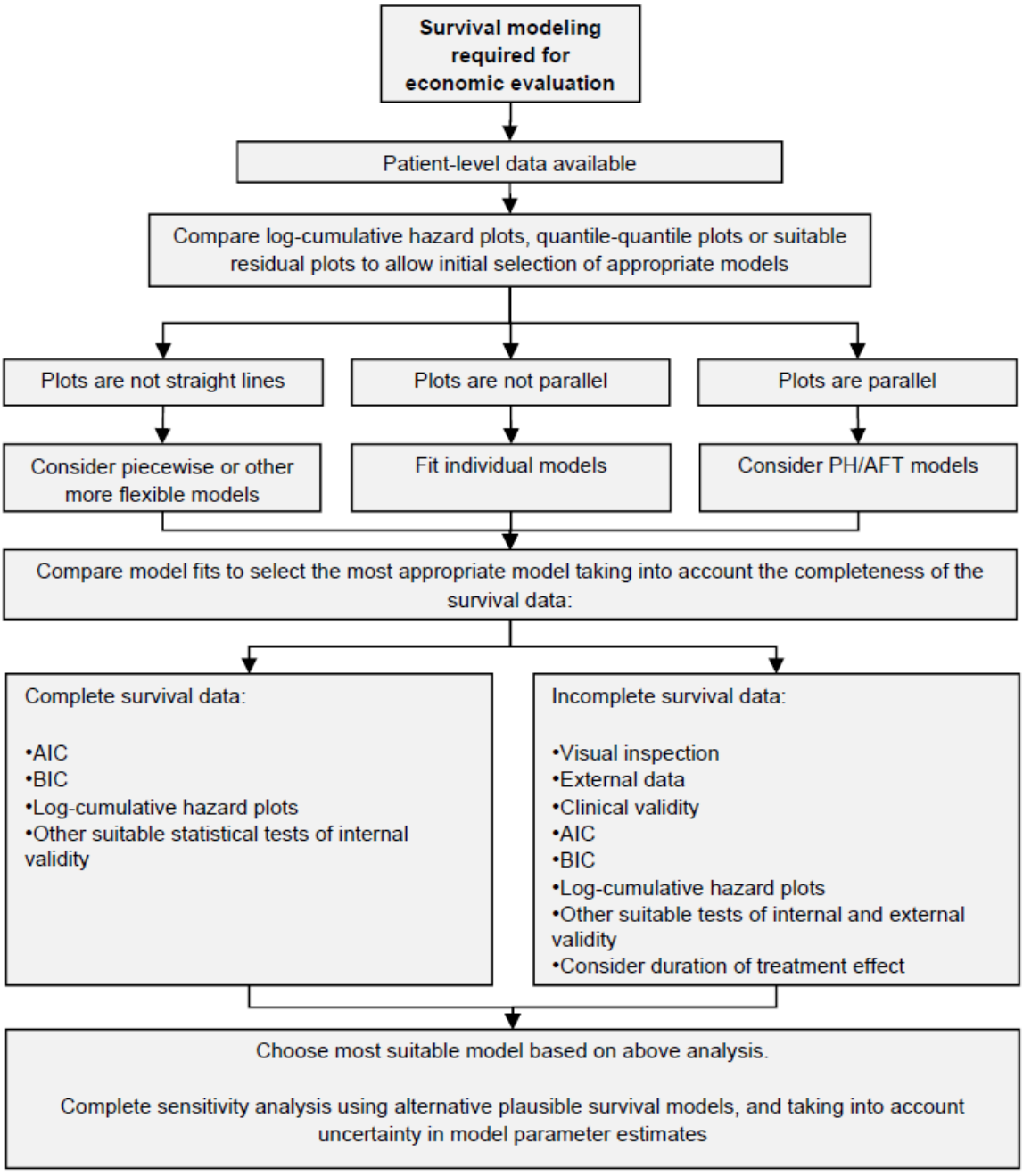
Figure 21. NICE TSD DSU 14 survival model selection process algorithm[129]



Abbreviations: AFT, accelerated failure time; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PH, proportional hazard

B.3.3.1.2 AEGEAN EFS data (AEGEAN mITT population)

Prior to fitting of parametric survival models, the log-cumulative hazards plots, Schoenfeld residual plots and smoothed hazard plots were generated in order to assess the PHA (see Figure 22 and Figure 23).

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As noted in Section B.2.9.1 and Appendix N, from assessing the curves visually, the crossing of the log cumulative hazard plots and the shape of the smoothed hazards (with initially increasing hazards and then slowly decreasing hazards over time) indicated evidence of non-proportionality. Both treatment arms exhibited similar survival until the 3-month mark, after which a clear and sustained separation in favour of the perioperative durvalumab arm is shown (this separation in curves beyond 3 months aligns with the planned timing of the first RECIST scan post-randomisation, occurring after neoadjuvant therapy completion and prior to surgery). However, the Schoenfeld test indicated that the PHA may hold (p=0.411) over the entire trial duration. Further exploration as to the most appropriate survival modelling approach was required.

The hazard plots' shape favoured adopting piecewise extrapolations from 3 months onward to account for changes in hazards. As can also be seen from the cumulative hazard and smoothed hazard plots specifically, the 3-month time period is a turning point in terms of hazard function and aligns with the planned timing of the first RECIST scan post-randomisation in the AEGEAN trial. To capture changes pre- versus post-surgical assessments, a piecewise extrapolation using a 3-month cut-point (91.3 days) was explored. This approach better accounts for these changes in hazards compared to using standard parametric distributions throughout, as demonstrated in the extrapolated EFS over the trial duration in Appendix M. A piecewise 3m+ approach showcases an improved visual fit and reduced variability in the extrapolated period.

Furthermore, examining the log-cumulative hazard plot for the overall trial period (Appendix E) in comparison to the piecewise 3m+ approach (Figure 22) reveals that the latter has broadly parallel lines, indicating that the PHA holds for this time period.

Therefore, given the suitability of using piecewise extrapolations with a 3-month cut-off and confirmation of the PHA through the log-cumulative hazard plot, Schoenfeld test (Figure 22) and smoothed hazards (Figure 23) for this approach, data from the neoadjuvant PDC arm of the AEGEAN trial was employed for the initial 3 model cycles, each lasting 1 month, followed by subsequent extrapolation. The perioperative durvalumab EFS efficacy was modelled by applying a HR to the neoadjuvant PDC arm from 3 months onwards (see section B.3.3.1.4 for more details).

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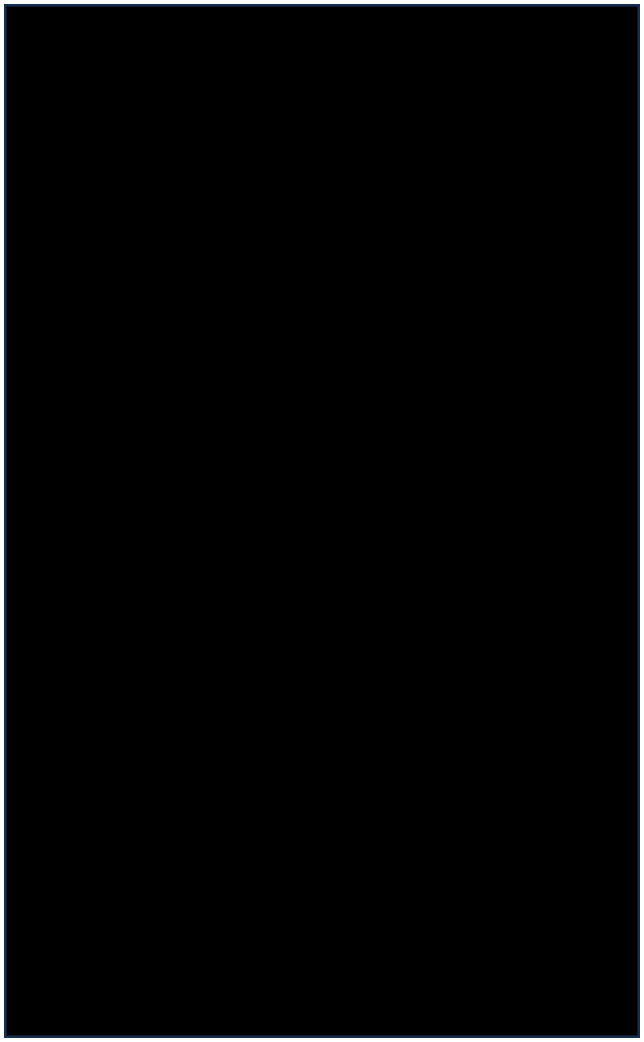
Figure 22. Log-cumulative hazard and smoothed Schoenfeld residuals plot for piecewise 3+ month interval; EFS



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

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Figure 23. Smoothed hazards plots for piecewise 3+ month interval; EFS

Abbreviations: EFS, event-free survival; SoC, standard of care

B.3.3.1.3 Neoadjuvant PDC from AEGEAN mITT population

As concluded above, the AEGEAN perioperative placebo arm was used to inform the efficacy of neoadjuvant PDC.

Statistical goodness of fit (AIC/BIC)

Statistical tests based on AIC and BIC scores (Table 32) were used to identify the best-fitting parametric distribution from month 3 onwards based on internal validity. The log-logistic distribution was the best statistically fitting distribution for the neoadjuvant PDC arm (in terms of AIC and BIC). However, all models with a difference of less than 4 points compared to the model with the lowest AIC were considered to provide a good relative statistical fit to the data (Weibull, lognormal, loglogistic, Gompertz, and generalised gamma).

Table 32. Goodness of fit statistics for AEGEAN neoadjuvant PDC; EFS (post-3 months)

Neoadjuvant PDC				
Model	**AIC**	**AIC Rank**	**BIC**	**BIC Rank**
Exponential	1019.2	6	1023.1	6
Weibull	983.2	2	990.8	2
Log-normal	985.2	4	992.8	3
Log-logistic	**982.3**	**1**	**989.9**	**1**
Gompertz	992.9	5	1000.6	5
Generalised gamma	984.3	3	995.8	4

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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. Model fits for neoadjuvant PDC are presented in Figure 24. All parametric distributions appear to provide reasonable fits, except for the exponential distribution. Therefore, based on the statistical and visual fit, the exponential model was not considered appropriate for the base case analyses.

Figure 24. 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

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 25 illustrates that the EFS predictions from all models were in line with the observed EFS from AEGEAN, apart from the Gompertz model which overestimates the proportion of patients remaining event free in the long term. Therefore, based on long-term extrapolations, the Gompertz model was not considered appropriate for the base case analyses.

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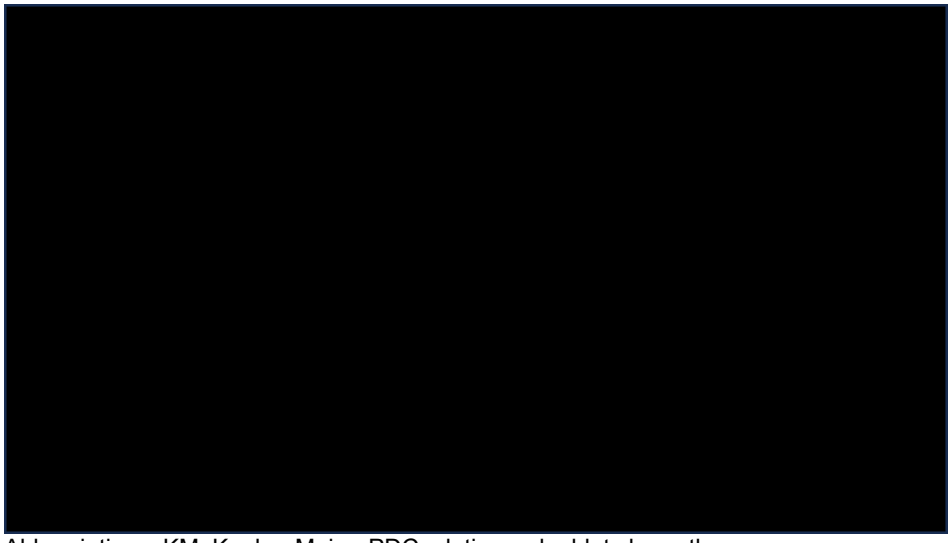
Figure 25. Long-term predictions; modelled EFS versus observed EFS from AEGEAN



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

Based on the good visual fit and similar statistical fit based on AIC for all models (apart from exponential and Gompertz), selection of the EFS extrapolation for the base case was informed by clinical expert opinion and external data to ensure clinical plausibility of extrapolations in the long-term.

Clinical plausibility of long-term extrapolations

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, clinicians were provided with EFS data at intervals of 6, 12, 24, 36, 48, and 60 months for the Weibull, log-normal, log-logistic, and generalized gamma models (refer to Table 33).

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 38% of patients event free at 60 months.[22] All other survival extrapolations were considered to underestimate the proportion of patients event free at 5 years and therefore were not deemed clinically plausible.

Based on the above, the log-normal was determined to be the most appropriate model to use in the base case analyses.

Table 33. Event-free survival landmarks (Neoadjuvant PDC)

EFS landmarks up to 60 months						
	6 months	12 months	24 months	36 months	48 months	60 months
Kaplan-Meier	79%	64%	52%	43%	-	-
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EFS, event-free survival

External validation

Due to uncertainty in predictions beyond the trial's follow-up, the EFS long-term projections underwent additional validation using external data.

The neoadjuvant PDC arm from the AEGEAN trial was compared to the pooled 5-year data on neoadjuvant chemotherapy sourced from the NSCLC Collaborative Group meta-analysis (MACG), which was also employed for comparative purposes in TA876. Table 34 shows a landmark comparison between the EFS data derived from the AEGEAN KM, log-normal model and NSCLC MACG 2014.[64]

The credibility of the meta-analyses was considered to be uncertain due to its inclusion of studies conducted in 2007 or before. Additionally, it comprises a substantial proportion (49%) of Stage IA-IB patients, who typically exhibit higher EFS rates than individuals in a Stage II-IIIB population (AEGEAN trial population).

Clinical experts in a UK advisory board conducted in January 2024, considered this source to underestimate EFS at 5 years for patients receiving neoadjuvant PDC. However, they did state that the source is dated (2014), therefore may lack robustness.[22]

NSCLC MACG was considered to provide more optimistic results than CheckMate-816 for the neoadjuvant PDC arm in TA876.[50] Consequently, the base case long-term extrapolation for the neoadjuvant PDC arm in TA876 did not align with the estimates derived from this study.[50]

Table 34. Neoadjuvant PDC EFS Validation: Landmark comparison

Source	Year 1	Year 2	Year 3	Year 4	Year 5
AEGEAN (IA1) EFS KM – PBO + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Predicted EFS – neoadjuvant PDC arm using log-normal	[redacted]	[redacted]	[redacted]	[redacted]	38%
NSCLC MACG 2014[64] †	[redacted]	[redacted]	[redacted]	[redacted]	36%

† EFS Landmarks for Years 1-4 are based on the digitization of the EFS KM curve from the meta-analysis. EFS at Year 5 is directly reported in the publication.[64]
Abbreviations: Durva, durvalumab; EFS, event-free survival; IA1, first data-cut; KM, Kaplan-Meier; MACG, meta-analysis Collaborative Group; NSCLC, non-small cell lung cancer; PBO, placebo; SoC, standard of care

Furthermore, in TA876, the company presented 5-year EFS for neoadjuvant PDC between 25-28%, consistent with the Felip/Pless EFS constructed curve (27.4% at 5 years).[50] Submission details indicate that 6 clinicians agreed that the log-normal distribution (derived from the company model) predicted the most plausible 5-year EFS, which was within this specified range. The 5-year EFS predicted for the neoadjuvant PDC arm in AEGEAN by the

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Weibull model most closely aligns with the committee preferred 5-year EFS in TA876 (see Table 30).

As described above, the log-normal extrapolation preferred by clinical experts was selected for use in the base case analyses. As external data indicates lower proportions of patients expected to be event-free at 5 years, scenario analyses were conducted incorporating the log-logistic, generalised gamma and Weibull models. This approach reflects a consideration of varying perspectives, ensuring a comprehensive and robust evaluation.

Summary: base case and scenario selection in the AEGEAN mITT population

In summary, after evaluation of goodness-of-fit criteria, visual inspections, and validation through input from UK clinical experts and external data sources, the survival extrapolation that most closely aligned with the expectations of UK clinicians for EFS in patients receiving neoadjuvant PDC was selected for the base case analyses. Hence, the log-normal model was considered the most suitable for the neoadjuvant PDC arm in the base case.

For scenario analyses, the log-logistic distribution, identified as the best statistically fitting model, generalised gamma and Weibull models were explored. This decision was based on external data validation, indicating a lower proportion of patients being event-free at 5 years compared to the proportions anticipated by clinical experts.

The following parametric distributions were therefore considered:

- Neoadjuvant PDC
    - Base case: AEGEAN observed data (first 3 months) + log-normal from 3 months
    - Alternative: AEGEAN observed data (first 3 months) + log-logistic from 3 months
    - Alternative: AEGEAN observed data (first 3 months) + generalised gamma from 3 months
    - Alternative: AEGEAN observed data (first 3 months) + Weibull from 3 months

B.3.3.1.4 Perioperative durvalumab from AEGEAN

The perioperative durvalumab EFS efficacy was modelled by applying a HR to the neoadjuvant PDC arm. First, the efficacy was informed by the neoadjuvant PDC AEGEAN EFS KM data, given the absence of separation of EFS curves in AEGEAN and for consistency across model comparators (see Section B.3.3.1.5). 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 piecewise ITCs analyses (3+ months).

For the base case analysis, the MAIC-adjusted HR was used. This MAIC-adjusted HR was derived after weighting to match the baseline characteristics more closely in the CheckMate-816 trial as described in Section B.2.9.1 (note that the MAIC-adjusted KM data is provided in the model for validation purposes). The model predicted EFS for the perioperative

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durvalumab arm, the MAIC-adjusted KM data and the EFS landmarks are presented in Figure 26and Table 36, accordingly.

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. The model predicted EFS for the perioperative durvalumab arm and EFS landmarks are presented in Table 36 and Table 37, accordingly.

Table 35 provides an overview of the piecewise HRs used to inform the post-3 months EFS efficacy for perioperative durvalumab. The use of the alternative base case was explored as a scenario and the results are presented in Appendix Q.

Table 35. 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; CRT, chemoradiotherapy; EFS, event-free survival; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PDC, platinum-doublet chemotherapy

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Figure 26. 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 36. Event-free survival landmarks (Perioperative durvalumab – base case)

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

† based on AEGEAN weighted from the MAIC against CheckMate-816

Abbreviations: EFS, event-free survival

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Figure 27. Five-year modelled EFS versus observed EFS from AEGEAN (unweighted from the NMA) – alternative base case

Abbreviations: EFS, event-free survival

Table 37. Event-free survival landmarks (Perioperative durvalumab – alternative base case)

EFS landmarks up to 60 months						
	6 months	12 months	24 months	36 months	48 months	60 months
Kaplan-Meier	84%	73%	63%	59%	-	-
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EFS, event-free survival

B.3.3.1.5 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

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Neoadjuvant nivolumab + PDC (CheckMate-816)

In the absence of head-to-head trial evidence for the comparison of perioperative durvalumab versus neoadjuvant nivolumab + PDC, an ITC was conducted to enable a comparison. EFS efficacy for neoadjuvant nivolumab + PDC was determined based on the relative efficacy of neoadjuvant nivolumab + PDC versus PDC alone in CheckMate-816, which was used in the MAIC (as described in Section B.2.9.1). Although the MAIC resulted in HRs in favour of perioperative durvalumab in the first three months, the neoadjuvant nivolumab + PDC EFS efficacy was based on the neoadjuvant PDC EFS KM data from AEGEAN for this time period, given the absence of separation of EFS curves in the AEGEAN and Checkmate 816 studies during the first three months and for consistency across model comparators. From month three onwards, the EFS efficacy was modelled via a piecewise HR applied to the EFS curve of neoadjuvant PDC (Table 38).

Table 38. Piecewise (post-3 months) EFS comparator efficacy (neoadjuvant nivolumab + PDC)

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 EFS KM, as used in the MAIC

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

Surgery alone and adjuvant PDC

To enable the comparison of perioperative durvalumab versus surgery alone and adjuvant PDC, an ITC was conducted. An NMA in the AEGEAN mITT using random effects was performed to inform the EFS efficacy (Section B.2.9.2). In the first three months, EFS for surgery alone and adjuvant PDC was based on the neoadjuvant PDC EFS KM data from AEGEAN to ensure consistency across model comparators. 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 39).

Table 39. Piecewise (post-3 months) EFS comparator efficacy (surgery alone and adjuvant PDC)

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

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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

B.3.3.2 *Estimation of transition probabilities for competing events*

Competing risks need to be considered when deriving the transition probabilities for use in a multi-state model. When competing risks are involved, there is no longer the one-to-one relationship between the hazard and survival probabilities, that is, the hazard of a particular event cannot simply be derived from the probability of survival, because survival is based on a combination of two or more hazards rather than just one.

Therefore, the transition probabilities of leaving a health state are derived by calculating the total probability of leaving that health state and assigning a proportional probability to each transition. For all states, the transition probabilities were estimated using the following equation derived by Ades et al.[130]:

$$TP(t,\mu,i) = \frac{\lambda_i(t)}{\sum_{k=1\ to\ n}\lambda_i(t)} \times (1 - e^{-(\sum_{k=1\ to\ n}\lambda_i(t))})$$

Where t is the time since entry of state, μ is the one-month cycle period, $\lambda_i(t)$ is the cause-specific hazard rate for outcome i, and n is the total number of events from each state (n=3 for EF [TP1, TP2, TP3], n=2 for LRR [TP4 and TP5] and n=1 for DM [TP6]). The cause-specific hazard is the instantaneous rate of failure due to cause i and was modelled using parametric survival models fitted to time-to-event data. For example, for EFS this would be:

Total probability = exp (- sum[hazard TP1 + hazard TP2 + hazard TP3])

Transition probability TP1 = hazard TP1 / sum(hazard TP1 + hazard TP2 + hazard TP3) * Total probability

B.3.3.3 *Modelling of EFS (TP1, TP2 andTP3)*

Data from AEGEAN are the primary source for the cost-effectiveness analysis, whereby perioperative durvalumab (intervention arm) is compared to neoadjuvant PDC (placebo arm) in patients with resectable NSCLC (stages IIA to IIIB).

The transition probabilities for TP1 (EF → LRR), TP2 (EF → DM) and TP3 (EF → Death) were calculated as follows:

- TP1 (EF → LR) = Non-death EFS event multiplied by the probability of the event being LRR
- TP2 (EF → DM) = Non-death EFS event multiplied by the probability of the event being DM

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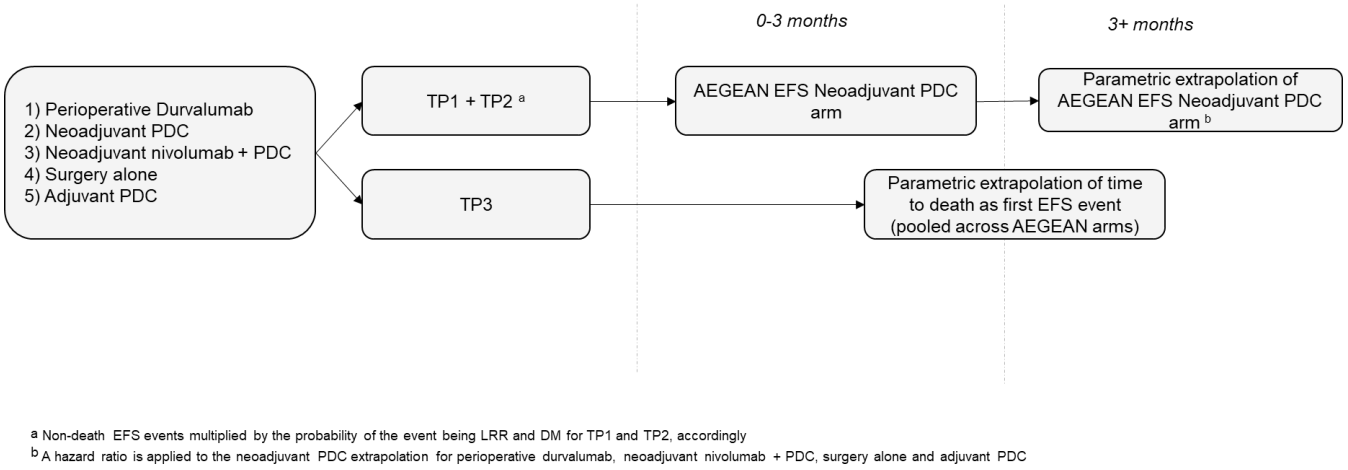
- TP3 (EF → Death)= max(Time to death as first EFS event, probability of death among the general population in the UK)

The same inputs and assumptions for the proportion of non-death EFS events being LRR or DM, and time to death as first EFS event have been used across all comparators. Therefore, the only treatment effect that has been explicitly included in the model is for EFS, in line with the ITCs which were conducted. Figure 28 provides a summary of the EFS (TP1, TP2 and TP3) modelling. Further details are provided in the following sections.

Figure 28. Diagram of EFS modelling



[a] Non-death EFS events multiplied by the probability of the event being LRR and DM for TP1 and TP2, accordingly
[b] A hazard ratio is applied to the neoadjuvant PDC extrapolation for perioperative durvalumab, neoadjuvant nivolumab + PDC, surgery alone and adjuvant PDC

Abbreviations: EFS, event-free survival; PDC, platinum-doublet chemotherapy; TP, transition probability

B.3.3.3.1 TP1 and TP2: Event-free (EF) to LRR or DM

Within each cycle, the probability to transition from EF to LRR (TP1) and from EF to DM (TP2) was calculated based on the estimated probability of an EFS event being either an LRR event or a DM event, having accounted first for the probability of an EFS event being death (see Section B.3.3.3.2).

Six 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. [22] 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. They suggested that a more accurate representation of clinical reality would involve reversing the proportions compared to the reported findings.[22] This clinical opinion was incorporated into the base case analysis with a [redacted] probability of transitioning to LRR and a [redacted] probability of transitioning to DM if a non-death EFS event occurs (Table 40). An alternative scenario was explored using the proportions derived from the AEGEAN study (see Table 40).

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.

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Table 40. Site of recurrence inputs for EF

Treatment arm	Site of recurrence events		Justification
	% LRR	% DM	
Base-case			
Perioperative durvalumab	[redacted]	[redacted]	UK clinician validation[22]
Neoadjuvant PDC (and all non-AEGEAN comparators)	[redacted]	[redacted]	
Scenario 1:			
Perioperative durvalumab	[redacted]	[redacted]	AEGEAN EFS by site of recurrence data (pooled across treatment arms in line with TA823)[23]
Neoadjuvant PDC (and all non-AEGEAN comparators)	[redacted]	[redacted]	

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

B.3.3.3.2 TP3: Event-free (EF) to Death

For the transition from EF to death, EFS data from AEGEAN (i.e., time to death as first EFS event) were used. Due to the relative immaturity of the AEGEAN trial data to populate this transition ([redacted], the data from the perioperative durvalumab and neoadjuvant PDC arms were pooled.

Standard parametric distributions were applied, in order to extrapolate the pooled time to death as first EFS event data. 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 to ensure consistency with the EFS extrapolation.

To ensure that patients do not live longer than the general population, the parametric distributions were adjusted to ensure that the hazards of the extrapolations could not be less than the General Population Mortality (GPM) hazards, using UK life tables.[131] For all modelled comparators (including non-AEGEAN comparators), time to death was assumed to be equal to that predicted using the pooled AEGEAN data.

Figure 29 shows the model fits for the pooled data across the AEGEAN arms. Details describing the model selection process are provided in Appendix M.

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Figure 29. EF to Death (TP3) model fits, pooled

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

B.3.3.3.3 Cure assumption

As detailed in B.1.3.1, complete surgical resection represents a potentially curative outcome for early-stage NSCLC.[3] In general, following surgery (with or without adjuvant therapy), patients are monitored for disease recurrence over a period of 5 years. Several studies have demonstrated that the risk of recurrence peaks during the years immediately after surgery, but is considerably reduced by 5 years after surgery.[9,132-135] Some patients may still experience recurrence beyond 5 years after surgery, but the risk remains low.[36,136,137]

In previous NICE appraisals assessing early-stage NSCLC (TA761[59], TA823[23] and TA876[50]) the consensus among clinical experts is that patients with NSCLC remaining event/disease-free for five years are deemed functionally cured and subsequently discharged from their care. In addition, given that a small proportion of patients will still experience recurrence beyond 5 years, previous NICE appraisals (TA761[59] and TA876[50]) have established an assumption that 95% of patients would achieve cure. This aligns with the proportion of patients in Sonoda et al. 2019[34], as employed in TA823[23], who experience recurrence beyond 5 years, without experiencing it within the initial 5 years post-surgery.

Consistent with these assessments, it is anticipated that a proportion of patients undergoing surgery (with or without adjuvant therapy) based on the AEGEAN trial may be considered cured beyond a certain timeframe.[23,50,59]

Clinical expert feedback for cure assumption

The fundamental rationale for incorporating the concept of cure within the model hinges on its clinical plausibility and relevance. Clinicians specialising in NSCLC provided their perspectives on the assumption of cure during a UK advisory board in January 2024. The clinicians unanimously endorsed the plausibility of cure, deemed the 5-year timeframe

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appropriate, and agreed that a proportion of 90-95% of patients achieving cure was reasonable.[22]

Implementation of cure in model

To reflect anticipated clinical outcomes for patients undergoing curative-intent surgery, alignment with assumptions from prior NICE appraisals, and validation from UK clinicians (as discussed in preceding sections), the model incorporates a 5-year cure timepoint. Additionally, the model assumes that 95% of patients would achieve cure if they have not experienced an EFS event at 5 years.

Within the model, the implementation of the cure assumption involves maintaining an event-free status for patients until death, representing the proportion considered cured. The transition from EF to death (i.e., TP3) is based on the log-normal distribution fitted to pooled data or GPM (as described in section B.3.3.3.3). For the proportion of patients not assumed to be cured, the model incorporates transitions to LRR and DM, as well as Death, utilising EFS extrapolations.

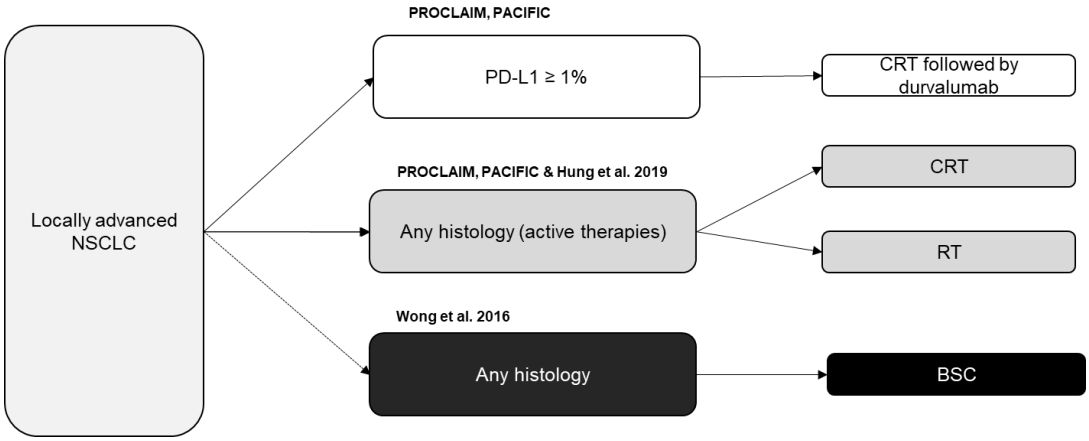
To assess the impact of varying the timing of the cure point (e.g., influenced by the duration of adjuvant therapy received) and the assumed proportion of cured patients (based on alternative sources used in TA823[23]), scenario analyses were conducted (refer to Section B.3.9.3).

B.3.3.4 *Modelling from locoregional recurrence (LRR) (TP4 and TP5)*

Patients in the LRR health state can either progress to the metastatic (DM) state (TP4) or transition to the death state (TP5). These transitions are individually modelled for each treatment arm and are dependent on the specific treatments received in LRR for each arm.

Treatment options in LRR include CRT followed by durvalumab, radiotherapy (RT) alone, or best supportive care (BSC) (refer to Figure 30).These treatment options are based on TA761,[59] with the inclusion of RT alone (as per external assessment group [EAG] feedback) and addition of CRT followed by durvalumab. The latter also represents an option for patients being considered for IO treatment and who are being treated with definitive CRT for locally advanced disease.

Figure 30. Treatment pathway in locally advanced NSCLC



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Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy, NSCLC, non-small cell lung cancer; PD-L1, programmed cell ligand-death 1; RT, radiotherapy

B.3.3.4.1 TP4: LRR to DM

Patients progressing from LRR enter the DM state (i.e., the event is assumed to be metastatic). Due to limited post-recurrence follow-up data available from AEGEAN, the probability of moving to this state was determined from clinical trials in locally advanced NSCLC (specifically the PACIFIC and PROCLAIM trials).[3,117,118]

- The PACIFIC trial is a phase III trial investigating CRT followed by durvalumab versus CRT as maintenance therapy in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based CRT.[118]
- The PROCLAIM trial is a phase III, open label RCT in adults with stage IIIA/B non-squamous NSCLC investigating etoposide-cisplatin with RT versus pemetrexed-cisplatin with RT.[3,117]

It was not considered appropriate to utilise data from the PACIFIC trial alone, since the timing of randomisation in PACIFIC to either durvalumab or placebo was after the patients had received CRT (approximately two months). Therefore, data from the PROCLAIM trial (etoposide + cisplatin arm) was used to model the initial period on entry in to the LRR health state (i.e., for the duration of CRT), and data from the PACIFIC trial was utilised for long-term extrapolations thereafter. To reflect the NICE recommendation for durvalumab as a consolidation therapy after CRT, the PACIFIC data used in the model were based on those patients with PD-L1 expression >=1%.

Specifically, the transition probabilities for the first two months from LRR entry were based on digitised PFS data from PROCLAIM. From month 3 onwards, the transitions were informed by time to progression (TTP) data from PACIFIC, as used in the state transition model included in the NICE appraisal for durvalumab as a consolidation therapy after CRT (TA798).[127] In TA798, standard parametric distributions were applied to the PACIFIC data. Based on visual inspection of the extrapolations, clinical plausibility and goodness-of-fit, the generalised gamma was chosen for extrapolating TTP. This is consistent with the NICE committee preferred extrapolation in TA798.[127] The combination of data from PROCLAIM and extrapolated TTP from PACIFIC were used to derive the probability of progression to DM from LRR for CRT followed by durvalumab and for CRT alone.

For patients who received RT in LRR, a HR was applied to the predicted PFS of CRT using data from the Hung et al. 2019 meta-analysis (CRT versus RT) to estimate PFS for RT.[138]Although there is a difference in efficacy between CRT and RT, it was assumed that the proportion of PFS events categorised as ‘progression’ (TP4) in each cycle was the same for RT as observed in CRT from the PACIFIC trial (Table 41).

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Table 41. Hazard ratio for RT alone vs. CRT based on meta-analysis by Hung et al. 2019[42]

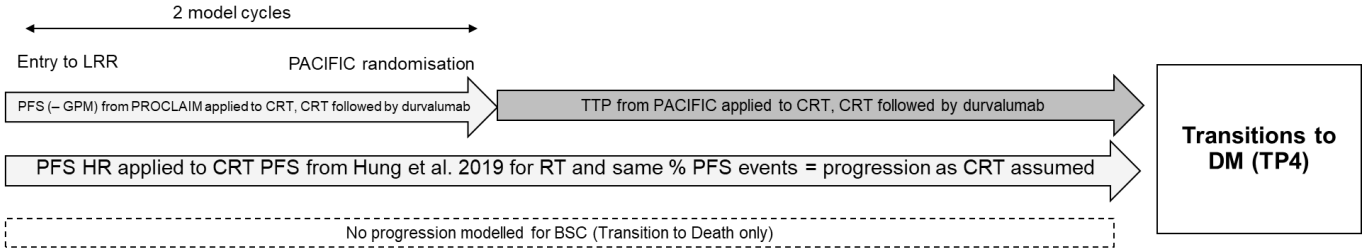
Hazard ratio	Lower limit (95% CI)	Upper limit (95% CI)	Source
1.37	0.12	1.67	Hung et al. 2019 (inverted published HR and CIs)[42]

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; HR hazard ratio; RT, radiotherapy.

An assumption was made that those patients who received BSC in LRR (20.5% in all treatment arms based on Wong et al. 2016)[12] would transition to the death state directly (i.e., not transition to DM and receive further treatment) (see Section B.3.3.4.2 describing TP5b).

Figure 31 provides an overview of the data and the assumptions used to model the transition from LRR to DM (i.e., TP4).

Figure 31. Overview of modelling from LRR to DM (TP4)



Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; HR, hazard ratio; GPM, general population mortality; PFS, progression-free survival; RT, radiotherapy; TP, transition probability

Weighted survival curve

The specific treatment received in the LRR health state impacts the transition probability to the subsequent DM health state. Of the remaining non-BSC treated patients in the LRR health state, patients can receive CRT followed by durvalumab, RT alone or CRT. Inclusion in the weighted survival cure is contingent on receiving one of these treatments.

With the inclusion of CRT followed by durvalumab as a treatment option in LRR, the distribution of LRR treatments in the perioperative durvalumab and neoadjuvant nivolumab + PDC arms was different for patients who were eligible for IO retreatment in LRR and for those who were not. Based on clinical feedback in TA823[23] and TA876,[50] and UK clinical expert input from an advisory board,[22] retreatment with IO is expected in clinical practice for patients who have received IO in the neoadjuvant or adjuvant resectable setting and have not progressed/experienced recurrence within 6 months of completing the previous IO therapy.[139]

Therefore, in the base case it was assumed that a proportion of patients who received perioperative durvalumab or neoadjuvant nivolumab + PDC in the EF health state are retreated with an IO therapy (i.e., CRT followed by durvalumab) in the LRR health state. In order to be retreated with IO therapy, patients should not have progressed within 6 months

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after completion of either IO treatments, i.e., after 21 months for perioperative durvalumab and after 8 months for neoadjuvant nivolumab + PDC.

For all patients who receive perioperative durvalumab in the EF health state and enter the LRR health state before month 21, no IO retreatment is permitted (LRR treatment distribution based on 'No IO retreatment' in Table 42), whereas IO retreatment is permitted for patients who enter the LRR health state in subsequent months (LRR treatment distribution based on 'IO retreatment' in Table 42).

The distribution of treatments in the LRR health state are presented in Table 42. The following weights were derived based on specific considerations: Firstly, the availability of CRT followed by durvalumab was restricted to patients exhibiting PD-L1 expression levels >= 1%, which constituted approximately 66.6% of patients in AEGEAN. Secondly, an assumption was made that among those eligible patients (i.e., PD-L1 >=1%), approximately 70% would receive CRT followed by durvalumab. This estimation was aligned with assumptions outlined in the TA798 resource impact template.[140] Lastly, for patients not receiving CRT followed by durvalumab, it was assumed that 82% would receive CRT, while the remaining 18% would receive RT alone. This assumption mirrored the proportion used in TA761.[59] Table 42 presents the active treatment options available (note that BSC is not an active treatment).

For the non-AEGEAN comparators, IO comparators (i.e., neoadjuvant nivolumab + PDC) were assigned the same treatment distributions as perioperative durvalumab, and non-IO comparators (i.e., surgery alone and adjuvant PDC) the same as neoadjuvant PDC.

Table 42. Survival curve weights based on treatments received in LRR

EF treatments (columns) LRR treatments (rows)	Perioperative durvalumab		Neoadjuvant PDC	Reference to section in submission
	No IO retreatment	IO retreatment		
CRT followed by durvalumab	0.0%	46.6%	46.6%	Section B.3.5.3.1
RT	82.0%	43.8%	43.8%	Section B.3.5.3.1
CRT	18.0%	9.6%	9.6%	Section B.3.5.3.1

Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; IO, immuno-oncology; LRR, locoregional recurrence; PBO, placebo; RT, radiotherapy.

B.3.3.4.2 TP5: LRR to death

To ensure clarity within the model, a distinction has been established between patients transitioning to death from LRR after receiving active treatment (i.e., TP5a), and those transitioning to death from LRR after receiving BSC (i.e., TP5b).

For TP5a, the transition from LRR to death was informed using GPM data from the UK life tables for the first two months.[131] From month 3 onwards, the transitions were informed by Company evidence submission for durvalumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for resectable non-small-cell lung cancer [ID6220]

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pre-progression survival (PrePS) in PACIFIC,[118] which was estimated based on the difference between PFS and TTP extrapolations, as per the approach used in TA798 (please refer to the description for TP4 in section B.3.3.4.1).[127]

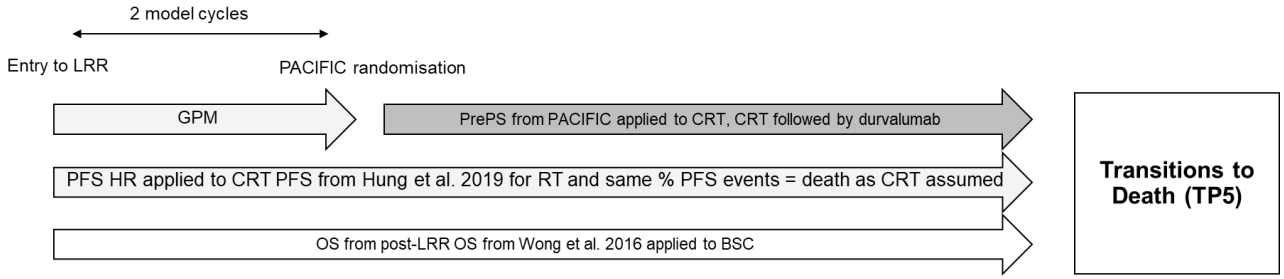
The extrapolation of PACIFIC TTP data is described for TP4 above. Standard parametric distributions were also applied to the PFS data. For consistency with the base case approach in TA798, based on visual inspection, clinical plausibility and goodness-of-fit based on AIC/BIC scores, the generalised gamma was selected for extrapolating PFS.[127]

Patients who underwent RT had their PFS estimated by applying a HR (Hung et al. 2019 meta-analysis[138]) to the predicted PFS for CRT (using data from Hung et al. 2019)[138], as outlined in TP4. Subsequently, the probability of death before progression (TP5) was determined based on the proportion of PFS events in each cycle that did not qualify as 'disease progression' events (TP4).

TP5b leverages data from Wong et al. 2016 sourced from the National Cancer Database, reporting OS post-recurrence for patients with local recurrence post-resection who received BSC.[12]

Figure 32 provides an overview of the data and the assumptions used to model the transition from LRR to death (i.e., TP5a and TP5b).

Figure 32. Overview of modelling from LRR to death (TP5)



Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; HR, hazard ratio; GPM, general population mortality; PFS, progression-free survival; RT, radiotherapy; TP, transition probability

For TP5b, in order to select the most suitable distribution to model BSC, the statistical goodness of fit based on AIC/BIC scores (Table 43) and visual fits (Figure 33) were examined. The log-normal provided the best statistical fit and a good visual fit to the observed data; therefore, this distribution was selected as the most appropriate for the base case analysis.

For each LRR treatment option, the probability of death in each cycle was constrained by GPM using UK life tables.[131]

Table 43. Goodness of fit statistics; BSC; LRR to Death (TP5b)

Model	AIC	AIC Rank	BIC	BIC Rank
Exponential	1319.0	6	1322.3	6
Weibull	1244.8	4	1251.4	4
Log-normal	**1228.0**	**1**	**1234.7**	**1**

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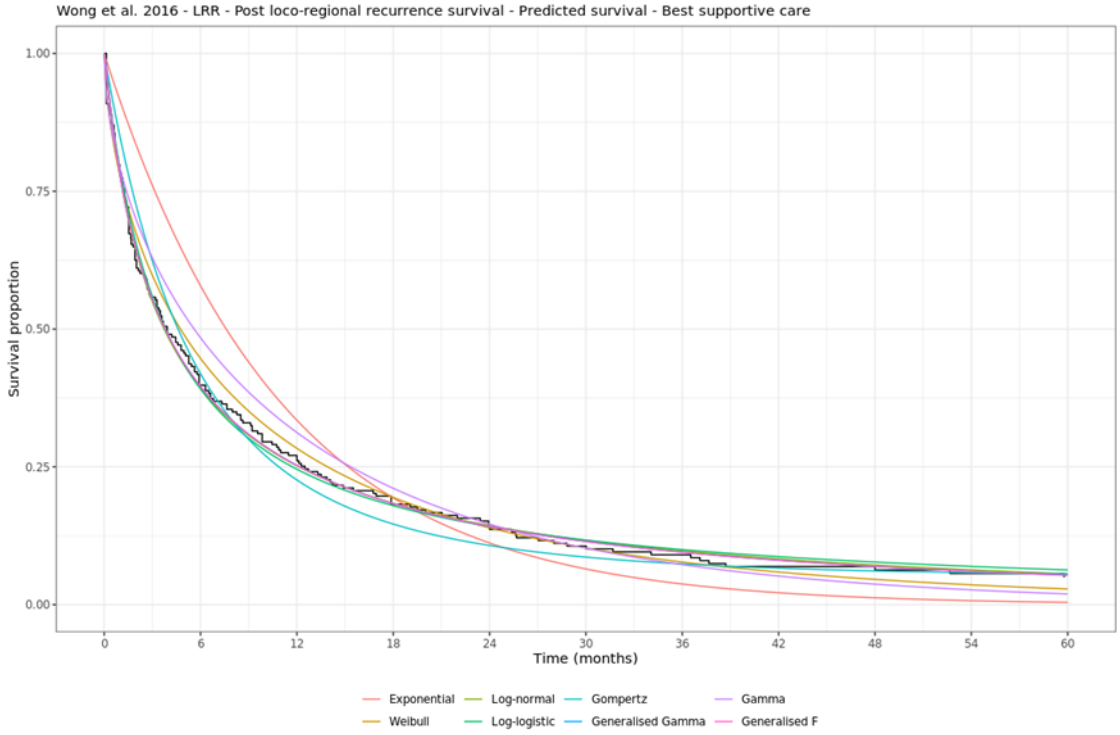
Log-logistic	1233.1	3	1239.7	2
Gompertz	1248.9	5	1255.5	5
Generalised Gamma	1230.0	2	1240.0	3

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

Figure 33. LRR to Death (TP5b); BSC, model fits



Weighted survival curve

The weighted survival curve for TP5 followed the same approach as described in Section B.3.3.4.1, with the exception that for TP5, survival was also impacted by patients who received BSC as an LRR treatment option. The final weighted TP5 survival curve amalgamated the weighted TP5a survival for active therapy (derived from the same distributions used for TP4, and clinical inputs as detailed for TP5a) and the TP5b survival for BSC (based on OS data from Wong et al. 2016).[12] This amalgamation was weighted according to the proportion of patients assumed to receive BSC post-local recurrence, estimated at 20.5% based on Wong et al. 2016.[12] This assumed proportion of patients receiving BSC in LRR was equivalent irrespective of the treatment received in the EF health state.

The distribution of treatments in the LRR health state used for modelling TP5 are presented in Table 44.

Table 44. Survival curve weights based on treatments received in LRR

EF treatments (columns) LRR treatments (rows)	Perioperative durvalumab		Neoadjuvant PDC	Reference to section in submission
	No IO retreatment	IO retreatment		

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BSC (no treatment)	**20.5%**		**20.5%**	Section B.3.5.3.1
Non-BSC (on treatment)	**79.5%**		**79.5%**	Section B.3.5.3.1
CRT followed by durvalumab	0.0%	46.6%	46.6%	Section B.3.5.3.1
RT	82.0%	43.8%	43.8%	
CRT	18.0%	9.6%	9.6%	

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

B.3.3.5 *Modelling of Distant Metastases (TP6)*

From DM, the probability of transitioning to death relied on the use of a nested partitioned survival model (PSM). This approach captures the impact of progression within the DM state in terms of costs and HRQoL, as well as the effect of treatments received within the DM state in terms of LYs and QALYs. PFS and OS data from the pivotal clinical trials of SoC were used to partition time to death into two tunnel states: progression-free within DM (DM1) and progressed disease within DM (DM2). The PFS and OS data were extrapolated, and weighted average PFS and OS curves were obtained based on the treatment market shares assigned in the DM state. DM1 was informed by PFS, whilst DM2 was informed by the difference between OS and PFS (i.e., post-progression survival or PPS). This approach distinguished costs and QALYs accrued pre- and post-progression. A depiction of the nested PSM approach is presented in Figure 34.

The main advantage of this approach for modelling DM compared with the use of separate health states for pre- and post-progression in DM (DM1 and DM2, respectively; as per TA671 and TA823), is that PFS and OS data can be used. These are more readily available from the literature compared with time-to-progression or pre-progression survival data, which would be required for transitions between and from the DM1 and DM2 health states (in TA671 for example, individual patient-level data were available from the FLAURA trial for modelling efficacy in the DM setting). Secondly, the modelling of costs and outcomes based on a nested PSM will allow the model to replicate the treatment pathway more closely and ensure consistency compared with previous HTAs of first-line treatments in metastatic NSCLC, which have all used PSM's based on PFS and OS.[123,126,128,141].

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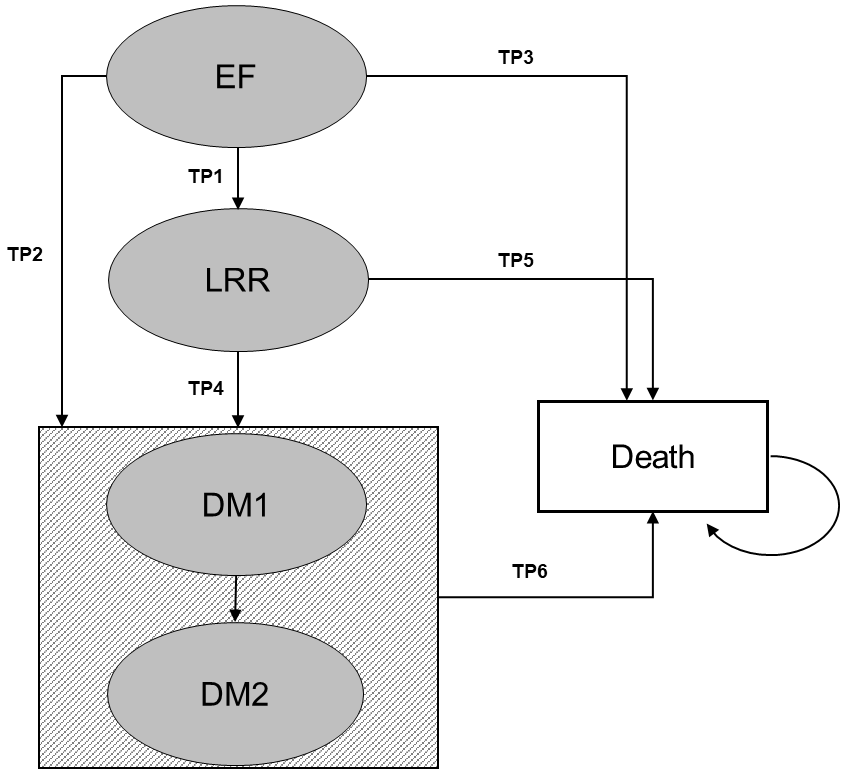
Figure 34. Model structure with nested partitioned approach for the DM state



Abbreviations: EF, event-free; DM, distant metastasis; LRR, locoregional recurrence; TP, transition probability.

In alignment with the treatment pathway for first-line mNSCLC (refer to Figure 35), the treatment pathway that informs modelling of DM was determined based on either active therapy or non-active therapy (i.e., BSC). For active therapies, the treatment pathway for first-line, metastatic NSCLC varies according to PD-L1 expression (with IO monotherapy recommended as a treatment option for PD-L1 ≥50%) and tumour histology (squamous and non-squamous disease), as per the treatment algorithm presented in NG122.[3] The treatment options for the different patient types included in the model are presented in Figure 35 and were validated by clinicians in an UK advisory board conducted in January 2024.[22]

IO treatments for first-line, metastatic NSCLC include pembrolizumab and atezolizumab:

- Pembrolizumab has been recommended by NICE in the first-line, metastatic setting as monotherapy for patients with PD-L1 ≥50% (TA531) and in combination with platinum-based chemotherapy for patients with squamous (TA770) and non-squamous (TA683) tumour histology.[123,126,128]
- Atezolizumab has been recommended by NICE in the first-line, metastatic setting as monotherapy for patients with PD-L1≥50% (TA705) and in combination with bevacizumab, paclitaxel and carboplatin for patients with non-squamous (TA584) tumour histology.[142,143]

For patients receiving active therapy on entry to DM, PFS and OS inputs from the following trials were utilised: KEYNOTE-024 (phase III RCT; PD-L1 ≥50%; pembrolizumab),[119] KEYNOTE-189 (phase III RCT; non-squamous; pembrolizumab + PDC, placebo + PDC),and KEYNOTE-407 (phase III RCT; squamous; pembrolizumab + PDC, placebo + PDC), which

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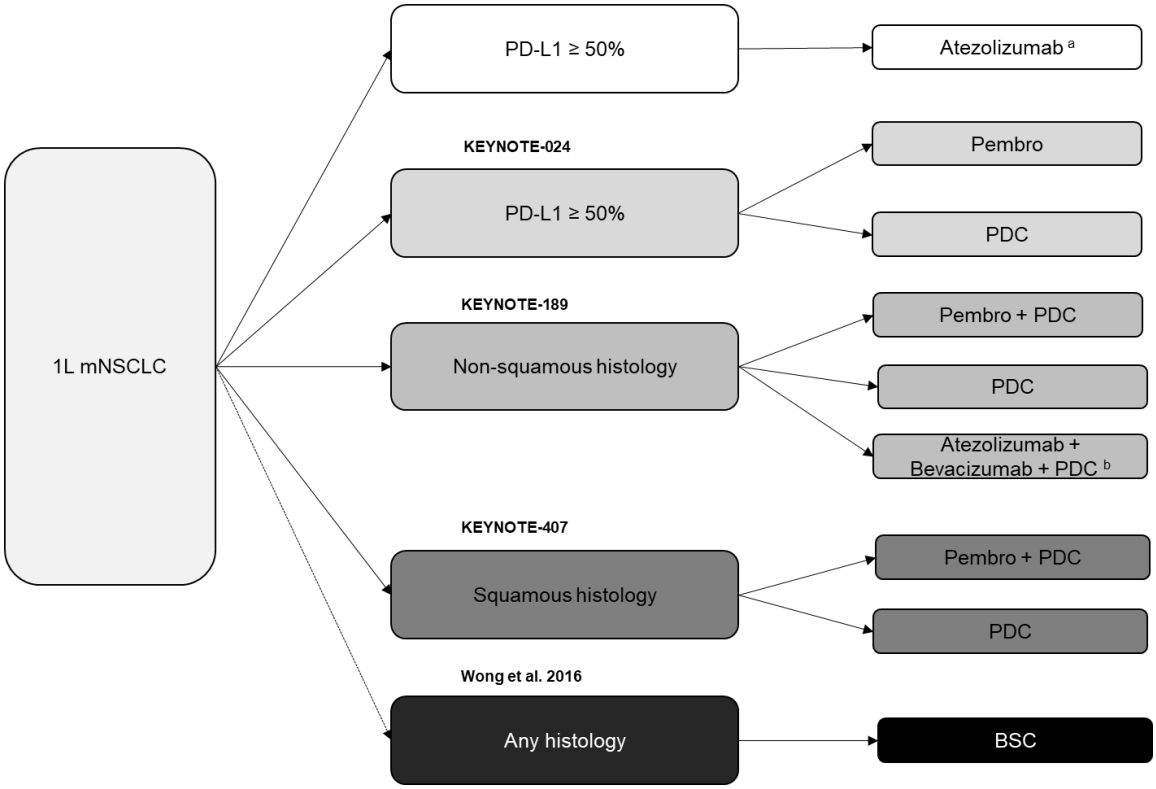
represent the pivotal trials for each of the pembrolizumab regimens and the primary sources of evidence used in TA531, TA683 and TA770, respectively.[116,123,126,128]

In the model, equivalent efficacy was assumed between 1) pembrolizumab monotherapy and atezolizumab monotherapy, 2) pembrolizumab combination therapy (for non-squamous histology) and atezolizumab combination therapy (for non-squamous histology). Therefore, the same PFS and OS data from the relevant KEYNOTE trials were utilised for treatments assumed to have equivalent efficacy. This simplifying approach aligns with TA705, where equivalent efficacy was assumed across the two IO treatments by employing a cost-minimisation modelling approach. [143]

For patients entering DM and receiving BSC, the efficacy data was drawn from Wong et al. 2016 (National Cancer Database).[12] This source, utilised for modelling transitions from LRR to death for BSC in LRR (section B.3.3.4.2), also provides information on OS post-recurrence for individuals experiencing distant recurrence after resection and receiving BSC.

The OS post-recurrence data from Wong et al. 2016 was therefore used to model transitions from DM to death.[12] As per LRR, patients receiving BSC in DM could only transition directly to the death health state (i.e., it was assumed that there would be no subsequent therapy after progression).

Figure 35. Treatment pathway in first line mNSCLC



[a] Equivalent efficacy to Pembro in KEYNOTE-024 is assumed

[b] Equivalent efficacy to Pembro + PDC arm in KEYNOTE-189 is assumed

Abbreviations: 1L, first-line; BSC, best supportive care; mNSCLC, metastatic non-small cell lung cancer; PDC, platinum-doublet chemotherapy; PD-L1, programmed cell ligand-death 1

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Standard parametric distributions were applied for the 8 treatment options in DM, to both PFS (active treatments, excluding BSC) and OS (all treatments). All transitions to death were corrected for general background mortality, estimated from UK life tables accounting for the age and gender distribution of the cohort.[131]

In extrapolating PFS and OS for active therapies, the AEGEAN model relies on the latest data extracted from the pivotal trials corresponding to each pembrolizumab regimen (see Table 45).[119,141,144] The preferred (non-piecewise) extrapolations used in the original NICE TAs were selected. In cases where a piecewise approach was utilised, the curves with the best statistical fits, as determined by AIC/BIC, were selected. The selection of data from these trials and the adoption of preferred extrapolations were carefully selected to closely replicate the predicted LYs and QALYs from previous NICE TAs.

For the OS extrapolation for BSC from Wong et al. 2016,[12] the log-normal distribution was selected because it had the best statistical fit and provided a good visual fit to the observed data. More details regarding the AIC/ BIC and extrapolation methods are available in Appendix M.

Table 45. Overview of the DCO and extrapolations used in the NICE appraisals and AEGEAN for the pembrolizumab regimens

Clinical trial - NICE TA	DCO used in NICE TA	Extrapolation used in NICE TA	DCO used in AEGEAN model	Extrapolation in AEGEAN model
KN189 - TA683 (CDF)	Final analysis (20 May 2019)[120]	OS: loglogistic (pembrolizumab arm) PFS: Piecewise extrapolation - KM data up to week 21 followed by Weibull (pembrolizumab arm)	5-year analysis (8 March 2022)[141]	OS: lognormal (pembrolizumab arm and atezolizumab arm) PFS: loglogistic (pembrolizumab arm and atezolizumab arm)
KN407 - TA770 (CDF)	Final analysis (09 May 2019)[121]	OS: loglogistic (both arms) PFS: Piecewise extrapolation - KM data up to week 26 followed by lognormal (both arms)	5-year analysis (23 February 2022)[144]	OS: loglogistic (pembrolizumab combination therapy (squamous) and PDC arm (squamous)) PFS: lognormal (pembrolizumab combination therapy (squamous) and PDC arm (squamous))
KN024 - TA531 (CDF)	Final analysis (10 July 2017)[119]	OS: Piecewise extrapolation - KM data up to week 33 followed by exponential (both arms) PFS: Piecewise extrapolation - KM	5-year analysis (1 June 2020)[119]	OS: loglogistic (pembrolizumab combination therapy (non-squamous) and PDC arm (non-squamous) and atezolizumab combination therapy (non-squamous))

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		data up to week 27 followed by exponential (both arms)		PFS: loglogistic (pembrolizumab combination therapy (squamous) and PDC arm (squamous) and atezolizumab combination therapy (non-squamous))

Abbreviations: CDF, Cancer Drug Fund; DCO, data cut-off; KM, Kaplan-Meier; KN, Keynote; NICE, National Institute of Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TA, technology appraisal

For each treatment arm, weighted average PFS and OS curves were calculated based on treatments received in DM; more details can be found in Section B.3.5.3.3.

B.3.3.5.1 Weighted survival curves

Weighted PFS

The treatments administered upon entering the DM health state, which influenced the efficacy of the DM health state, have an impact on the overall predicted PFS. A weighted average of the extrapolated PFS curves from the relevant trials,[119-121] was calculated based on the treatment distributions assigned for DM1. It was assumed that patients in this state could receive pembrolizumab (either as monotherapy or in combination therapy), atezolizumab (as monotherapy or in combination therapy), chemotherapy alone, or BSC. Patients receiving BSC in the DM state were presumed to transition directly to death and were thus excluded from the weighted PFS analysis.

The distribution of treatments in the DM health state related to PFS are presented in Table 46 (reflecting the treatment choice in DM1). The distribution of treatments in the perioperative durvalumab arm and neoadjuvant nivolumab + PDC arm differs depending on whether patients were retreated with IO or not (as previously described for modelling transitions from LRR). In line with clinical practice in the UK, detailed in TA823 and TA876,[23,50] to be retreated with IO (i.e., pembrolizumab/ atezolizumab monotherapies or combination therapies) patients should not have progressed within 6 months after completion of durvalumab or nivolumab treatment in the EF health state, i.e., after 21 months for perioperative durvalumab and after 8 months for neoadjuvant nivolumab + PDC. Therefore, in the model, for all patients who received perioperative durvalumab in the EF health state and entered the DM health state before month 21, no IO retreatment was permitted (DM treatment distribution based on 'No IO retreatment' in Table 44), whereas IO retreatment was permitted for patients who entered the DM health state in subsequent months (DM treatment distribution based on 'IO retreatment' in Table 46).

Section B.3.5.3.3 provides more detail regarding the distribution of treatments applied to perioperative durvalumab and neoadjuvant PDC arms in the DM state. In summary, a proportion of patients who received active therapy on entering the DM health state were assumed to receive IO therapy (based on the TA683 and TA770 resource impact templates),[145,146] and of these, the proportion of patients receiving pembrolizumab/ atezolizumab monotherapies or combination therapies (histology-specific), was determined

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by the proportion of patients in AEGEAN with PD-L1≥50% and the proportion of patients with non-squamous/squamous histology. The distribution for patients receiving pembrolizumab versus atezolizumab in each setting was determined using IPSOS data.[147] For the IO comparators (i.e., neoadjuvant nivolumab + PDC), they were assigned the same treatment distributions as perioperative durvalumab, and non-IO comparators (i.e., surgery alone and adjuvant PDC) were assigned the same as neoadjuvant PDC.

Table 46. PFS curve weights based on treatments received in DM

EF treatments (columns) DM treatments (rows)	Perioperative durvalumab		Neoadjuvant PDC	Reference to section in submission
	No IO retreatment	IO retreatment		
Pembrolizumab	0%	20%	20%	B.3.5.3.3.1.
Pembrolizumab + PDC (non-squamous)	0%	23%	23%	B.3.5.3.3.1.
Pembrolizumab + PDC (squamous)	0%	28%	28%	B.3.5.3.3.1.
Atezolizumab	0%	3%	3%	B.3.5.3.3.1.
Atezolizumab + bevacizumab + PDC (non-squamous)	0%	6%	6%	B.3.5.3.3.1.
PDC (non-squamous)	51%	10%	10%	B.3.5.3.3.1.
PDC (squamous)	49%	10%	10%	B.3.5.3.3.1.
BSC	N/A	N/A	N/A	B.3.5.3.3.1.

Abbreviations: BSC, best supportive care; DM, distant metastasis; IO, immuno-oncology; PDC, platinum-doublet chemotherapy

Weighted OS

Applying a similar methodology as PFS, treatments received in DM have a direct impact on predicted overall survival. Patients in DM1 could receive pembrolizumab monotherapy, pembrolizumab combination therapy, atezolizumab monotherapy, atezolizumab combination therapy, chemotherapy alone, or BSC. A weighted average of the extrapolated OS curves from the relevant trials [119-121] and Wong et al. 2016[12], was calculated, based on the assigned treatment distributions.

The distribution of treatments in the DM health state for OS are presented in Table 47. These are used to obtain a weighted OS curve, which is subsequently utilised in combination with the weighed PFS curve to calculate the treatment options in DM2. Although patients in DM who were administered BSC were excluded from the weighted PFS calculation, they were considered in the weighted OS calculation. The distribution of treatments therefore differs from those applied in PFS in the DM health state. As per the treatment distribution for LRR, the proportion of patients assumed to receive BSC on entry into the DM health state was based on Wong et al. 2016 (22.7%) and assumed to be equivalent regardless of which treatment was received in the EF health state.[12]

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Similar to PFS, a distinction was made between patients who were re-treated with IO and those who were not. The distribution of treatments varies between the perioperative durvalumab arm and the neoadjuvant nivolumab + PDC arm based on whether patients undergo retreatment with IO or not. Eligibility for IO retreatment, involving pembrolizumab or atezolizumab monotherapy, or combination therapy, depends on patients not progressing within 6 months post-completion of durvalumab or nivolumab treatment in the EF health state,[139] i.e., after 21 months for perioperative durvalumab and after 8 months for neoadjuvant nivolumab + PDC. In the model, for patients receiving perioperative durvalumab in the EF health state who transition to the DM health state before the 21-month mark, IO retreatment is not permitted (DM treatment distribution based on 'No IO retreatment' in Table 47). Whereas IO retreatment is permissible for patients entering the DM health state beyond this timeframe (DM treatment distribution based on 'IO retreatment' in Table 47).

For the IO comparators (i.e., neoadjuvant nivolumab + PDC), they were assigned the same treatment distributions as perioperative durvalumab, and for non-IO comparators (i.e., surgery alone and adjuvant PDC) they were assigned the same as neoadjuvant PDC.

Table 47. OS curve weights based on treatments received in DM

EF treatments (columns) DM treatments (rows)	Perioperative durvalumab		Neoadjuvant PDC	Reference to section in submission
	No IO retreatment	IO retreatment		
Pembrolizumab	0%	16%	16%	B.3.5.3.3.1.
Pembrolizumab + PDC (non-squamous)	0%	17%	17%	B.3.5.3.3.1.
Pembrolizumab + PDC (squamous)	0%	22%	22%	B.3.5.3.3.1.
Atezolizumab	0%	2%	2%	B.3.5.3.3.1.
Atezolizumab + bevacizumab + PDC (non-squamous)	0%	5%	5%	B.3.5.3.3.1.
PDC (non-squamous)	39%	8%	8%	B.3.5.3.3.1.
PDC (squamous)	38%	8%	8%	B.3.5.3.3.1.
BSC	23%	23%	23%	B.3.5.3.3.1.

Abbreviations: BSC, best supportive care; DM, distant metastasis; IO, immuno-oncology; PDC, platinum-doublet chemotherapy

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B.3.4 *Measurement and valuation of health effects*

B.3.4.1 *Health-related quality-of-life data from clinical trials*

B.3.4.1.1 Methods

Patients with NSCLC have impaired HRQoL compared to the general population, and the negative impact of NSCLC on patients QoL can be further pronounced if patients have one or more chronic comorbidities in addition to the lung cancer symptoms. In order to capture the impact of treatment with perioperative durvalumab on patients' QoL in the trial, HRQoL was assessed in AEGEAN using the EuroQol five dimensions, five-level questionnaire (EQ-5D-5L) (Section B.2.6.4). [148]

As per protocol, EQ-5D-5L questionnaires were administered at baseline; at each treatment visit during the neoadjuvant treatment period (i.e., weeks 0, 3, 6, and 9); at pre-surgical assessment (within 30 days of surgery); at the first treatment visit during the adjuvant treatment period; 30 days (±3 days) after the last dose of study treatment; and at months 2, 3 and 6 (±1 week) after the last dose of study treatment following completion or discontinuation of study treatment.

B.3.4.1.2 Mapping

In line with NICE guidance,[58] the EQ-5D-5L responses collected in the AEGEAN trial were 'cross walked' to produce EQ-5D-3L derived UK utility values using the Hernández Alava et al., 2017 algorithm.[122] The scores used were taken from the mITT analysis set of AEGEAN, consisting of all completed EQ-5D-5L measures (i.e., excluding EQ-5D-5L observations with any missing domain responses). As HRQoL was assessed in AEGEAN during the neoadjuvant phase, the AEGEAN EQ-5D data were considered for the EF health state only. For other health states (i.e., LRR, DM1 and DM2), either assumptions were used or HRQoL inputs from the literature were implemented.

Mixed models for repeated measures (MMRM) method was used to estimate the statistical relationship between utilities and health state (defined by recurrence or treatment status). This method accounts for the autocorrelation in utility score within each patient and is appropriate when handling data that are missing at random. Specifically, a random intercept model assuming independent within-subject errors was fitted to account for the subject variability. Estimation was based on restricted maximum likelihood method.

Univariate and multivariate analyses were conducted by fitting models including each of the covariates listed below (i) separately, (ii) together with treatment received, and (iii) their interaction:

- (Randomised) Treatment
- Recurrence status (pre-recurrence, post-recurrence)
- Treatment + Recurrence status

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- Treatment + Recurrence status + Treatment * Recurrence status (Both terms and their interaction included)

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

1) Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
2) Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
3) Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
4) Toeplitz – as above for number 2, but each visit shares the same variance.
5) Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

B.3.4.1.3 Utility results

A total of [redacted] EQ-5D-5L observations were collected from 699 patients. Among these, [redacted] observations were documented before progression or recurrence in [redacted] patients, [redacted] observations were recorded after progression or recurrence in [redacted] patients, and [redacted] observations 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 48. The pre-recurrence estimate across pooled treatment arms was used in the cost-effectiveness model to represent the EF health state utility. Due to the low number of observations recorded post-recurrence, the same utility values to the EF health state were used for the LRR health state. 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 48. EQ-5D utility index (UK weights)

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.

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B.3.4.2 *Health-related quality-of-life studies*

A de novo SLR was conducted to identify HRQoL evidence in resectable Stage I-III NSCLC. The methods and results are discussed in Appendix H.

B.3.4.3 *Health-related quality of life data used in the cost-effectiveness analysis*

Utility values from AEGEAN were estimated for the EF health state. However, due to limited follow-up data in AEGEAN, alternative sources and assumptions were used to inform subsequent health state utilities. For the LRR health state, utilities were sourced from TA798,[127] which were derived using the EQ-5D data from the PACIFIC trial. This value is very similar to the utility value for the EF health state, aligning with TA761.[59] Utility values for the DM health state were sourced from TA683, which were derived using the EQ-5D data from the KEYNOTE-189 trial.[123]

The included health state utility values were assumed to be equivalent across treatments (i.e., utilities were not treatment-specific). Clinicians in an UK advisory board validated the utility values.[22] An overview of the utilities used in the cost-effectiveness model is presented in Table 49.

Table 49. Summary of health state utility values

Health state	Utility value	SE
EF	[redacted]	[redacted]
LRR	[redacted]	[redacted]
DM1	0.759	0.076
DM2	0.662	0.066

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

The utility values from AEGEAN used in the EF health state were higher ([redacted]) than the age-adjusted utility value for the UK general population (0.829).[122] To explore the impact of the utility values obtained from AEGEAN compared to UK population norms, a scenario whereby the EF utility was capped at 0.829 was assessed (see Section B.3.9.3). In addition, alternative utility values for EF were tested in scenario analyses based on Andreas et al. 2018 identified in the HRQoL SLR,[14] and in line with TA761 (see Table 50 for an overview).[59]

Table 50. Alternative utility estimates used in the base case and scenario analysis

	EF	LRR	DM1	DM2
Base case	[redacted]	[redacted]	0.759	0.662
Description	AEGEAN EQ-5D (EQ-5D-5L AEGEAN EQ-5D-5L	PACIFIC EQ-5D (as per TA798)[127]	KEYNOTE-189 EQ-5D (as per TA683)[123]	KEYNOTE-189 EQ-5D (as per TA683) [123]

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			cross walked to EQ-5D-3L)			
Scenario			0.72	[redacted]	0.759	0.662
Description	Andreas et al. 2018[14]	PACIFIC EQ-5D (as per TA798)[127]	KEYNOTE-189 EQ-5D (as per TA683)[123]			KEYNOTE-189 EQ-5D (as per TA683) [123]

Abbreviations: DM1, distant metastasis (pre-progression); DM2, distant metastasis (post-progression); EF, event-free; LRR, locoregional recurrence.

B.3.4.4 *Adverse reactions*

The cost-effectiveness model takes into account adverse reactions resulting from grade 3 or 4 AEs which occurred in more than 5% of patients during the neoadjuvant and/or adjuvant treatment phases in the AEGEAN trial. Disutilities associated with these AEs were integrated into the model to capture the decline in patients' HRQoL caused by treatment-related AEs.

The total mean QALY loss associated with AEs for each treatment was determined by calculating the treatment-specific AE frequencies, the mean utility decrements related to these AEs, and the mean AE duration of each. Disutilities occurring because of AEs were applied in the first model cycle only, since it is reasonable to assume that treatment-related AEs are most likely to occur shortly after initiating a new therapy.

HRQoL decrements due to AEs were not available from AEGEAN. Therefore, disutility values were sourced from Nafees et al., 2008,[149] in line with in NICE TA876.[50] The study by Nafees et al. 2008 considered HRQoL, as measured by EQ-5D, in patients with metastatic NSCLC. Where no data was available, assumptions on utility decrements were made.

The AE disutilities values applied in the cost-effectiveness model are presented in Table 51.

Table 51. AE disutility values

Adverse event	Disutility	Source
Neutropenia	-0.007	Nafees et al. (2008)[149] - as per TA876[50]
Neutrophil count decreased	-0.007	Assumed the same as neutropenia
Anaemia	-0.007	Assumed the same as neutropenia - as per TA876[50]

Abbreviation: TA, technology appraisal

B.3.4.5 *Age adjustment*

An age adjustment was applied to the utility values in the CEM based on the latest DSU report regarding the estimation of EQ-5D by age and sex in the UK.[150] This age adjustment approach is in line with TA876.[50] The report provides EQ-5D estimates stratified by age and sex from two sources: the 2014 Health Survey for England (HSE) and a large-scale UK survey conducted by the Economic Methods of Evaluation in Health and Social Care Policy

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Research Unit (EEPRU). The DSU recommends the use of estimates obtained by HSE as these were consistent with the published literature.

In the model, the EQ-5D-3L estimates using the HSE 2014 data were applied as the general population norms for the UK.[150] In line with TA876,[50] the first step of the calculation comprised of determining the baseline mean utility, i.e., utility at the starting age of the model (i.e., 64 years), based on the EQ-5D norms at this age weighted by sex. A multiplier was then applied to the mean utility value to each age by comparing its EQ-5D estimate with the reference utility. The utility adjustment value used in the model is presented in Table 52.

Table 52. Age-adjusted utility

Utility value	SE	Source
0.829	0.083	Hernandez et al. 2022 - Weighted utility at age 64 (i.e., AEGEAN mean age at baseline)[150]

Abbreviations: SE, standard error.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

The types of costs considered in the economic model include drug acquisition and administration costs related to the therapies received, costs related to management of the disease and terminal care, and AE-related costs. A summary of these cost categories is presented in Table 53.

Table 53. Overview of key cost components

Cost category	Description
Drug acquisition	Costs for intervention and comparator therapies. Treatment acquisition costs are dependent on dosing regimens and frequency of administrations, which differ for the neoadjuvant and adjuvant settings.
Drug administration	Costs for drugs administered intravenously.
Radiotherapy	Patients who receive radiotherapy have different costs depending on whether the radiotherapy is given as part of, post-operative radiotherapy or as a treatment option in the LRR health state.
Surgery	A one-time cost of surgical resection was considered for a proportion of patient's post-neoadjuvant treatment. Surgery costs are included as a weighted average of costs by surgery type (i.e., thoracotomy or minimally invasive surgery).
Treatment monitoring	Regular monitoring costs for laboratory tests are applied when patients receive a treatment.
Healthcare resource use	Healthcare resource use data relating to clinical visits, hospitalisation, and imaging for each of the alive model health states.
Terminal care	A one-time cost for end-of-life care is considered for patients who enter the Dead health state and is included as a weighted average of costs by terminal care setting (i.e., hospital, hospice or home care)

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AE management	One-time costs for grade 3 or 4 AEs occurring in more than 5% of patients in the AEGEAN trial are applied in the first model cycle.

Abbreviations: AE, adverse event; CRT, chemoradiotherapy; LRR, locoregional recurrence.

B.3.5.1 *Resource identification, measurement and valuation studies*

A de novo SLR was conducted to identify resource use and costs evidence in resectable Stage I-III NSCLC. The methods and results are presented in Appendix I.

B.3.5.1.1 Appropriateness of NHS Ref costs/PbR tariffs

NHS reference costs for 2021/2022 were used to model the costs of chemotherapy administration, radiotherapy, surgery, adverse events, laboratory tests, and healthcare resource use such as hospitalisation, clinical visits, and imaging procedures.

B.3.5.2 *Intervention and comparators' costs and resource use*

B.3.5.2.1 Treatment acquisition cost for patients in EF health state

3.5.2.1.1 Treatment acquisition cost of neoadjuvant treatment

The cost of neoadjuvant treatment is relevant for durvalumab and the array of different PDC received in AEGEAN during the neoadjuvant phase. Table 54 presents the distribution of PDC for each neoadjuvant treatment. In the perioperative durvalumab and neoadjuvant PDC treatment arms, the distribution of PDC was based on the AEGEAN mITT data. For patients in the neoadjuvant nivolumab + PDC arm, all patients received nivolumab and PDC, with the distribution of the specific PDC agents informed by CheckMate-816,[66] considering the patients' non-squamous and squamous histology.

Table 54. Distribution of PDC in the neoadjuvant setting across comparators

PDC types		Durva + PDC[a]	Neoadjuvant PDC	Nivo + PDC[b]
Cisplatin +	Pemetrexed	15.7%	15.1%	39.6%
	Paclitaxel	0.0%	0.3%	0.0%
	Gemcitabine	11.5%	10.8%	38.6%
	Docetaxel	0.0%	0.0%	0.0%
Carboplatin +	Pemetrexed	39.4%	36.7%	0.0%
	Paclitaxel	30.7%	34.9%	21.8%
	Gemcitabine	2.7%	10.8%	0.0%
	Vinorelbine	0.0%	0.0%	0.0%
	Docetaxel	0.0%	0.0%	0.0%

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Abbreviations: Durva, durvalumab; nivo; nivolumab; PDC, platinum-doublet chemotherapy
a Patients in this treatment arm also received durvalumab.
b Patients in this treatment arm also received nivolumab.
c Patients in this treatment arm also received radiotherapy.

Costs were assigned for 4 full cycles of neoadjuvant treatment in the perioperative durvalumab and neoadjuvant PDC arms, and 3 cycles of neoadjuvant treatment in the neoadjuvant nivolumab + PDC arm .

Neoadjuvant treatment costs for all therapies were calculated based on the time to discontinuation of treatment (TDT) data from AEGEAN (DCO 10 November 2022). For outside-trial comparators, assumptions were made to model the TDT. The AEGEAN KM analysis of the mITT population consisted of (i) time to study treatment discontinuation or death and (ii) time to neoadjuvant PDC treatment discontinuation or death. The KM plots for the time to discontinuation of perioperative durvalumab and perioperative placebo (i.e., neoadjuvant PDC arm) per AEGEAN arm are presented in Figure 36 and Figure 37.

It is important to highlight that the TDT data covers both the neoadjuvant and adjuvant treatment phases. Consequently, inputs for the duration of neoadjuvant and adjuvant treatments determine the appropriate cycle the relevant costs were allocated.

Figure 36. Time to treatment discontinuation of perioperative durvalumab (KM Plot)

DCO 10 November 2022

Abbreviations: SoC, standard of care

Source: AstraZeneca 2023[151]

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Figure 37. Time to treatment discontinuation of neoadjuvant PDC (KM Plot)

DCO 10 November 2022

Abbreviations: SoC, standard of care

Source: AstraZeneca 2023[151]

Additional information about the assumptions used to inform the TDT for both AEGEAN and non-AEGEAN treatments are shown in Table 55.

Table 55. Overview of the assumptions used to inform the TDT in the neoadjuvant setting

Treatment arm	TDT assumptions
Perioperative durvalumab	• Durvalumab cost: Costs were derived from the durvalumab TDT included in the AEGEAN perioperative durvalumab arm • PDC cost: Costs were derived from the neoadjuvant PDC TDT included in the AEGEAN perioperative durvalumab arm
Neoadjuvant PDC	• PDC cost: Costs were derived from the neoadjuvant PDC TDT included in the AEGEAN perioperative placebo (i.e., neoadjuvant PDC) arm
Neoadjuvant nivolumab + PDC	• Nivolumab cost: Costs were derived from the durvalumab TDT included in the AEGEAN perioperative durvalumab arm

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Treatment arm	TDT assumptions
	• PDC cost: Costs were derived from the neoadjuvant PDC TDT included in the AEGEAN perioperative durvalumab arm. The difference in number of neoadjuvant treatment cycles between AEGEAN and CheckMate-816 is captured by the respective neoadjuvant treatment durations.

Abbreviations: CRT, chemoradiotherapy; PDC, platinum-doublet chemotherapy; SoC, standard of care; TDT, time to discontinuation of treatment.

3.5.2.1.2 Treatment acquisition cost of adjuvant treatment

Patients receiving perioperative durvalumab, neoadjuvant nivolumab + PDC and adjuvant PDC were treated with adjuvant treatment. Based on AEGEAN, all patients in the perioperative durvalumab arm who received adjuvant treatment were administered durvalumab monotherapy. In the neoadjuvant nivolumab + PDC arm, based on TA876,[50] a proportion of patients were assumed to receive adjuvant treatment after surgery. The adjuvant treatment options included PDC alone or RT (Table 56). Treatment costs were applied for the mean number of treatment cycles received in the adjuvant setting in CheckMate-816.[50] All patients in the adjuvant PDC arm received 3 cycles of PDC. Patients were assumed to be equally split across the different PDC regimens. Table 57 provides an overview of the distribution of different PDC regimens in the adjuvant setting for patients receiving neoadjuvant nivolumab + PDC and adjuvant PDC.

Table 56. Proportion of patients in the neoadjuvant nivolumab + PDC arm receiving adjuvant treatments

Treatment	% receiving adjuvant treatment	% receiving adjuvant systemic therapy (PDC)	% receiving adjuvant radiotherapy
Neoadjuvant nivolumab + PDC	19.9%	63.6%	25.7%

Abbreviations: PDC, platinum-doublet chemotherapy.

Table 57. PDC treatments received in the adjuvant setting

PDC type		Nivo + PDC[a]	Adjuvant PDC
Cisplatin +	Pemetrexed	10.7%	11.1%
	Vinorelbine	10.7%	11.1%
	Gemcitabine	10.7%	11.1%

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PDC type		Nivo + PDC[a]	Adjuvant PDC
	Docetaxel	10.7%	11.1%
Carboplatin +	Pemetrexed	31.5%	11.1%
	Paclitaxel	0.0%	11.1%
	Gemcitabine	0.0%	11.1%
	Vinorelbine	0.0%	11.1%
	Docetaxel	0.0%	11.1%

Abbreviations: PDC, platinum-doublet chemotherapy.
[a] In this arm, 25.7% of those receiving adjuvant treatment is receiving radiotherapy and the rest (74.3%) one of the PDC regimens listed above

Similar to how the neoadjuvant treatment costs were determined, adjuvant treatment costs were calculated using the number of patients on treatment, as per the TDT data from AEGEAN (DCO 10 November 2022). These are presented in Figure 36 and Figure 37 for perioperative durvalumab and perioperative placebo (i.e., neoadjuvant PDC), accordingly. Since the TDT data includes both the neoadjuvant and adjuvant periods, the adjuvant treatment duration inputs were used to determine the relevant cycles to apply the costs.

Additional information about the assumptions used to inform the TDT for both the AEGEAN and non-AEGEAN treatments where adjuvant costs were applicable are shown in Table 58.

Table 58. Overview of the assumptions used to inform the TDT in the adjuvant setting

Treatment arm	TDT assumptions
Perioperative durvalumab	• Durvalumab cost: Costs were derived from the durvalumab TDT included in the AEGEAN perioperative durvalumab arm
Neoadjuvant nivolumab + PDC	• PDC cost: Costs were derived from the neoadjuvant PDC TDT included in the AEGEAN perioperative placebo (i.e., neoadjuvant PDC) arm. The TDT data were rebased according to the percentage of patients remaining in the EF health state at the start of adjuvant therapy.
Adjuvant PDC	• PDC cost: Costs were derived from the neoadjuvant PDC TDT included in the AEGEAN perioperative placebo (i.e., neoadjuvant PDC) arm. The TDT data were rebased

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Treatment arm	TDT assumptions
	according to the percentage of patients remaining in the EF health state at the start of adjuvant therapy.

Abbreviations: PDC, platinum-doublet chemotherapy; SoC, standard of care; TDT, time to discontinuation of treatment.

B.3.5.2.2 Drug dose and unit costs for patients in EF health state

Drug dosing regimens per model cycle are presented in Table 59 for the intervention and comparators in the EF health state. The dose per treatment cycle was calculated based on the dose per administration, the number of administrations per treatment cycle, and the duration of the treatment cycle for each therapy. These were then adjusted based on the model cycle length.

Table 59. Dosing regimen per cycle in EF health state

Treatment in EF health state		Dose per administration		Frequency (per treatment cycle) [a]	Max administrations
Perioperative durvalumab (Neoadjuvant phase)	Durvalumab +	1500.0	mg	1	4
	Carboplatin	550.0	mg/mL/min	1	
	Pemetrexed	918.6	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Cisplatin	137.8	mg/m^2	1	
	Pemetrexed	918.6	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Carboplatin	660.0	mg/mL/min	1	
	Paclitaxel	367.4	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Carboplatin	550.0	mg/mL/min	1	
	Gemcitabine	2296.5	mg/m^2	2	
	Durvalumab +	1500.0	mg	1	4
	Cisplatin	137.8	mg/m^2	1	
	Paclitaxel	367.4	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Cisplatin	137.8	mg/m^2	1	
	Gemcitabine	2296.5	mg/m^2	2	
Neoadjuvant nivolumab + PDC	Nivolumab +	360.0	mg	1	3
	Cisplatin	137.8	mg/m^2	1	
	Pemetrexed	918.6	mg/m^2	1	
	Nivolumab +	360.0	mg	1	3
	Carboplatin	550.0	mg/mL/min	1	
	Paclitaxel	367.4	mg/m^2	1	
	Nivolumab +	360.0	mg	1	3
	Cisplatin	137.8	mg/m^2	1	
	Gemcitabine	2296.5	mg/m^2	2	
Perioperative durvalumab	Durvalumab	1500.0	mg	1	12

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Treatment in EF health state		Dose per administration		Frequency (per treatment cycle) [a]	Max administrations
(adjuvant phase)					
PDC [b, c]	Carboplatin +	550.0	mg/mL/min	1	4 (neoadj) 3 (adj)
	Pemetrexed	918.6	mg/m^2	1	
	Cisplatin +	137.8	mg/m^2	1	4 (neoadj) 3 (adj)
	Pemetrexed	918.6	mg/m^2	1	
	Carboplatin +	660.0	mg/mL/min	1	4 (neoadj) 3 (adj)
	Paclitaxel	367.4	mg/m^2	1	
	Cisplatin +	137.8	mg/m^2	1	4 (neoadj) 3 (adj)
	Gemcitabine	2296.5	mg/m^2	2	
	Cisplatin +	137.8	mg/m^2	1	4 (neoadj) 3 (adj)
	Paclitaxel	367.4	mg/m^2	1	
	Cisplatin +	137.8	mg/m^2	1	3 (adj)
	Vinorelbine	45.9	mg/m^2	2	
	Cisplatin +	137.8	mg/m^2	1	3 (adj)
	Docetaxel	137.8	mg/m^2	1	
	Carboplatin +	550.0	mg/mL/min	1	4 (neoadj) 3 (adj)
	Gemcitabine	2296.5	mg/m^2	2	
	Carboplatin +	550.0	mg/mL/min	1	3 (adj)
	Vinorelbine	45.9	mg/m^2	2	
	Carboplatin +	550.0	mg/mL/min	1	3 (adj)
	Docetaxel	137.8	mg/m^2	1	

Abbreviations: adj, adjuvant; CRT, chemoradiotherapy; EF, event-free; neoadj, m, minute; mg, milligram; mL, millilitre; neoadjuvant; PDC, platinum doublet chemotherapy.
[a] Treatment cycle length is 21 days for all treatments with a chemotherapy. For adjuvant monotherapy with durvalumab, the treatment cycle is 28 days.
[b] PDC can be administered either as neoadjuvant or adjuvant treatment. It may accompany IO or be administered on its own.

Average dosages for intravenous interventions were calculated using an average body surface area (BSA) of 1.84 m^2, obtained from the AEGEAN population combined with the Gehan and George formula (Table 60).[152] For the base case analysis, vial sharing for intravenous chemotherapy was assumed given that vial sharing is prevalent in NHS practice, therefore wastage costs were excluded.

Table 60. AEGEAN Patient characteristics informing the dosing calculations

Patient characteristics	Mean (SD)	Source
Age at baseline (years)	64.0 (0.32)	Heymach et al. 2023[20]
Weight (kg)	[redacted]	AEGEAN CSR[75]
Height (cm)	[redacted]	AEGEAN CSR[75]

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BSA (m^2)	[redacted]	AEGEAN CSR[75] (calculated using the Gehan and George formula and AEGEAN mITT patient characteristics)[152]

Abbreviations: BSA, body surface area; cm, centimetre; CSR, clinical study report; kg, kilogram; m, metre; SD, standard deviation.

Unit acquisition costs for the intervention and relevant comparators were sourced from the British National Formulary (BNF 2023)[153] and the electronic market information tool (eMIT)[85] databases and are displayed in Table 61. Durvalumab [redacted] per 500 mg vial.

Table 61. Unit acquisition costs

Treatment	Dose per vial (mg)	Cost per pack	Cost per mg	Source
Durvalumab [a]	120	[redacted]	[redacted]	*BNF 2023 (via NICE)[153]*
	500	[redacted]	[redacted]	*BNF 2023 (via NICE)[153]*
Carboplatin	150	£7.44	£0.08	*eMIT NPC code DHE001[85]*
	450	£14.69	£0.04	*eMIT NPC code DHE002[85]*
	50	£4.05	£0.10	*eMIT NPC code DHE003[85]*
	600	£21.54	£0.24	*eMIT NPC code DHE162[85]*
Cisplatin	100	£9.53	£0.11	*eMIT NPC code DHA010[85]*
	10	£2.42	£0.18	*eMIT NPC code DHA013[85]*
	50	£5.58	£0.10	*eMIT NPC code DHA011[85]*
Docetaxel	20	£3.68	£0.10	*eMIT NPC code DHC025[85]*
	80	£8.17	£0.03	*eMIT NPC code DHC029[85]*
	160	£16.04	£0.02	*eMIT NPC code DHC046[85]*
Gemcitabine	1200	£33.69	£0.02	*eMIT NPC code DHB246[85]*
	1400	£34.89	£0.02	*eMIT NPC code DYC085[85]*
	1600	£37.32	£0.02	*eMIT NPC code DHK055[85]*
	1800	£40.01	£0.02	*eMIT NPC code DHB247[85]*
Nivolumab	40	£439.00	£10.98	*BNF 2023 (via NICE)[153]*
	100	£1,097.00	£10.97	*BNF 2023 (via NICE)[153]*
	120	£1,317.00	£10.98	*BNF 2023 (via NICE)[153]*
	240	£2,633.00	£10.97	*BNF 2023 (via NICE)[153]*
Paclitaxel	100	£11.49	£0.11	*eMIT NPC code DHA145[85]*

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Treatment	Dose per vial (mg)	Cost per pack	Cost per mg	Source
	150	£17.28	£0.12	*eMIT NPC code DHA297*[85]
	300	£17.40	£0.06	*eMIT NPC code DHA210*[85]
	30	£4.03	£0.13	*eMIT NPC code DHA144*[85]
Pemetrexed	100	£29.11	£0.29	*eMIT NPC code DYC062*[85]
	500	£45.70	£0.09	*eMIT NPC code DYC063*[85]
	850	£49.93	£0.06	*eMIT NPC code DZV051*[85]
	1000	£81.30	£0.08	*eMIT NPC code DEI018*[85]
Vinorelbine	10	£74.45	£0.74	*eMIT NPC code DHA220*[85]
	50	£158.63	£0.32	*eMIT NPC code DHA221*[85]
No treatment/BSC	N/A	£0.00	£0.00	N/A

[a] Based on commercial access agreement

Abbreviations: BNF, British National Formulary; BSC, best supportive care; eMIT, electronic market information tool; NPC, national product classification.

B.3.5.2.3 Treatment administration costs

Drug administration costs were applied per administration for drugs given intravenously. Unit costs for drug administration were based on NHS Reference Costs 2021/2022.[154] For the first treatment cycle, a cost of £207.59 was applied for simple chemotherapies and £440.71 for complex chemotherapies. For all subsequent cycles, a cost of £326.46 was applied. For oral therapies, no administration cost was assumed, in line with TA823 and TA347.[23,155]

B.3.5.2.4 Cost of radiotherapy

Administration costs for RT were based on values reported in the NHS Reference Costs 2021/2022.[154] Costs per administration differ between RT given as part of post-operative CRT, and RT as a treatment option in the LRR health state. Unit costs used to calculate the cost of RT for patients in the model are presented in Table 62.

Table 62. Radiotherapy cost inputs

Item	Inputs			Sources	
	Unit cost per administration	Total costs (incl. monitoring costs	Resource use	Cost [a]	Resource use
Radiotherapy as a post-operative treatment					
Radiotherapy fractions	£394.00	£10,457.06	44 Gy in 22 fractions over 4.4 weeks	SC30Z - Deliver a fraction of intraluminal brachytherapy	Pless 2015 SAKK 16/00[154]

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Preparations	£1,789.08		1 meeting per cycle	SC53Z - Preparation for intraluminal branchytherapy	Assumption
Radiotherapy in the LRR state					
Radiotherapy fractions	£193.71	£6,890.71	60 Gy in 30 fractions over 6 weeks	SC23Z - Deliver a fraction of complex treatment on a megavoltage machine	NICE NG122, 1.4.31[3]
Preparations	£1,079.53		1 meeting per cycle	SC52Z - Preparation for complex conformal radiotherapy, with technical support	Assumption

Abbreviations: Gy, gray; LRR, locoregional recurrence; NICE, National Institute for Health and Care Excellence.
[a] Unit costs were sourced from the NHS Reference costs 2021/2022.[154]

B.3.5.2.5 Cost of surgery

The costs of surgery were estimated as a weighted average of costs according to surgery type (i.e., thoracotomy versus minimally invasive surgery). Unit costs of surgery for each surgical type were obtained from the NHS Reference Costs 2021/2022.[154]

The proportion of patients undergoing surgery after neoadjuvant durvalumab (81%) or after neoadjuvant PDC (81%) was informed by AEGEAN, whilst the proportion of patients undergoing surgery after neoadjuvant nivolumab + PDC (83%) was informed by the CheckMate-816 trial.[66] For patients receiving surgery alone or adjuvant PDC, all patients were assumed to receive the cost of surgery (100%).

The proportion of patients undergoing a thoracotomy compared to minimally invasive surgery was based on AEGEAN for perioperative durvalumab and neoadjuvant PDC. For patients receiving neoadjuvant nivolumab + PDC, the same proportion was assumed as for perioperative durvalumab. For patients receiving surgery alone or adjuvant PDC, the same proportion as neoadjuvant PDC was assumed. Table 63 presents the inputs used to estimate the costs of surgery.

Table 63. Surgery costs

Treatment (% undergoing surgery)	Surgery type	Unit cost[a]	% undergoing surgery type	Cost of surgery by treatment arm[b]
Perioperative durvalumab (81%)	Thoracotomy	£11,280.17	50%	£7,632
	Minimally invasive surgery	£3,983.38	50%	
Neoadjuvant PDC (81%)	Thoracotomy	£11,280.17	52%	£7,668
	Minimally invasive surgery	£3,983.38	48%	
	Thoracotomy	£11,280.17	50%	£7,632

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Treatment (% undergoing surgery)	Surgery type	Unit cost[a]	% undergoing surgery type	Cost of surgery by treatment arm[b]
Neoadjuvant nivolumab + PDC (83%)	Minimally invasive surgery	£3,983.38	50%	
Surgery alone (100%)	Thoracotomy	£11,280.17	52%	£7,768
	Minimally invasive surgery	£3,983.38	48%	
Adjuvant PDC (100%)	Thoracotomy	£11,280.17	52%	£7,768
	Minimally invasive surgery	£3,983.38	48%	

Abbreviations: PDC, platinum doublet chemotherapy.
[a] Unit costs were sourced from the NHS Reference costs 2021/2022: Thoracotomy (DZ02H-M weighted average, elective inpatient); Minimally invasive (DZ67Z, elective inpatient).[154]
[b] Costs of surgery by treatment were estimated by weighting the unit costs for surgery based on the proportion of surgery distribution.

B.3.5.3 *Subsequent health-state unit costs*

B.3.5.3.1 Treatment costs for patients in LRR health state

Treatment costs for patients in the LRR health state were estimated based on the individual costs of the LRR treatment options in the model, i.e., (i) CRT followed by durvalumab (PD-L1≥1%), (ii) CRT alone, (iii) RT alone, (iv) BSC.

The distribution of patients across the different treatment regimens largely depended on two pillars: 1) treatment at EF (IO or not) and 2) IO retreatment restrictions, i.e., whether patients who received IO at EF and had progressed within a specific timeframe after completion of IO therapy were retreated with IO. Different distributions were calculated based on the following:

1. Patients received IO treatment in EF, but retreatment is not possible (e.g., because they have progressed within 6 months after the last dose of IO therapy). Patients cannot therefore receive IO (CRT followed by durvalumab) in LRR. This is applicable for perioperative durvalumab and neoadjuvant nivolumab + PDC.
2. Patients have received IO treatment in EF and retreatment is permitted for patients who have not progressed within 6 months after the last dose of IO therapy. Thus, this proportion of patients can receive IO (CRT followed by durvalumab) in LRR. This is applicable for perioperative durvalumab and neoadjuvant nivolumab + PDC.
3. No IO treatment in EF; this is applicable for neoadjuvant and adjuvant PDC, neoadjuvant CRT and surgery alone (i.e., non-IO comparators). Patients are therefore able to receive IO (CRT followed by durvalumab) in LRR.

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The distribution of patients in LRR across the different treatment modalities was estimated as follows. First, the proportion of patients receiving BSC was informed by the proportion of patients receiving BSC following local recurrence in Wong et al. 2016. According to the TA798 resource impact template,[140] 70% of patients were assumed to receive active therapy, i.e., non-BSC. In this setting, active therapy is CRT followed by durvalumab (permitted only for patients with PD-L1≥1% and for patients without IO treatment at EF or with IO treatment at EF who are retreated). The remainder of patients eligible for active therapy were assigned to CRT or RT alone, based on 82% and 18% split, respectively, consistent with the approach in TA671.[59]

Patients not fulfilling the IO retreatment and PD-L1 criteria were not able to receive CRT followed by durvalumab. Table 64 presents an overview of the distribution of treatment modalities for patients in the LRR health state based on treatment received in EF.

Table 64. 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%	65.2%	14.3%	20.5%
IO (retreatment)	37.1%	34.8%	7.6%	20.5%
No IO	37.1%	34.8%	7.6%	20.5%
Assumptions	Only PD-L1 ≥1% eligible for IO	TA761 (ADAURA) assumed 82% RT and 18% CRT based on UK clinical expert opinion.[59] Same distribution used for those patients not receiving CRT followed by durvalumab[127] or BSC		Wong et al. 2016. % supportive care following local recurrence[12] 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.

Patients receiving BSC were assumed to transition directly to death (i.e., without subsequent progression to DM). Thus, these patients were modelled separately from those receiving active treatment, and the market shares were re-distributed across the rest of the treatment options accordingly. Table 65 presents the treatment shares after re-weighting.

Table 65. Treatment shares for LRR treatment modalities before and after re-weighting

	No IO retreatment allowed	**IO retreatment allowed**	**No IO**
Treatment	**Share of treatment**		

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CRT followed by durvalumab	0.0%	37.1%	37.1%
RT	65.2%	34.8%	34.8%
CRT	14.3%	7.6%	7.6%
Treatment	**Re-weighted (after removing the BSC proportion)**		
CRT followed by durvalumab	0.0%	46.6%	46.6%
RT	82.0%	43.8%	43.8%
CRT	18.0%	9.6%	9.6%

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

B.3.5.3.2 Drug dose and unit costs for the LRR health state

Drug dosing regimens per model cycle are presented in Table 66 for the LRR treatment modalities. Dose per treatment cycle was calculated based on the dose per administration, the number of administrations per treatment cycle, and the duration of the treatment cycle for each therapy, and then adjusted according to the model cycle length.

Average dosages for intravenous interventions were calculated based on an average BSA of 1.84 m^2 (as presented in Table 60). For the base case analysis, vial-sharing for intravenous chemotherapy was assumed to occur, therefore wastage costs were excluded.

Table 66. Dosing regimen per cycle in LRR health state

Treatment in LRR health state		Dose per administration (mg)		Frequency (per treatment cycle) [a]	Max administrations	Source
Durvalumab	Durvalumab	1500.0	mg	1	13	PACIFIC trial[118]
CRT	Cisplatin +	91.9	mg/m^2	1	2	PROCLAIM trial[117]
	Etoposide	91.9	mg/m^2	1		

Abbreviations: CRT, chemoradiotherapy; LRR, locoregional recurrence.
[a] Treatment cycle length is 28 days.

Unit acquisition costs were sourced from the BNF[153] and eMIT[85] databases, and are presented in Table 67. Durvalumab [redacted], resulting in a net price of [redacted] per 500 mg vial.

Table 67. Unit acquisition costs for the components of the LRR treatment options

Treatment	Dose per vial (mg)	Cost per pack	Cost per mg	Source
Durvalumab	120	[redacted]	[redacted]	*BNF 2023 (via NICE)[153]*
	500	[redacted]	[redacted]	*BNF 2023 (via NICE)[153]*
Cisplatin	100	£9.53	£0.11	*eMIT NPC code DHA010[85]*
	10	£2.42	£0.18	*eMIT NPC code DHA013[85]*
	50	£5.58	£0.10	*eMIT NPC code DHA011[85]*
Etoposide	100	£4.21	£0.04	eMIT NPC code DHA320[85]

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Treatment	Dose per vial (mg)	Cost per pack	Cost per mg	Source
	500	£16.69	£0.03	eMIT NPC code DHA250[85]
No treatment/BSC	N/A	£0.00	£0.00	N/A

Abbreviations: BNF, British National Formulary; BSC, best supportive care; eMIT, electronic market information tool.

To account for the different timings and durations of treatments within the same trial as well as to simplify the calculations, the individual components of the different treatment combinations were separated and placed in a treatment basket. For each treatment component, the duration, proportion of patients receiving the specific treatment, and costs were applied separately (considering the cumulative proportions of patients receiving each treatment across the treatment combinations). For example, chemotherapy applies to both the CRT followed by durvalumab and CRT alone as LRR treatment options. Notably, these proportions are cumulative across treatments and thus, unlike the treatment shares, do not sum to 100%.

Table 68 presents an overview of the treatment duration, proportion receiving each treatment from the treatment basket, as well as associated treatment acquisition and administration costs relevant for the LRR health state.

Table 68. Overview of treatment duration, costs and proportion of patients receiving LRR treatments from a treatment basket

Treatment basket	Duration (model cycle)	Proportion of patients receiving:		Treatment acquisitions costs per cycle	Admin costs per cycle
		No IO retreatment	IO retreatment		
Durvalumab	12.0	0.0%	46.6%	[redacted]	£207.59
Chemotherapy (Cisplatin + Etoposide)	1.8	18.0%	56.2%	£19.35	£440.71
Radiotherapy	18.0	100.0%	100.0%	£6,890.71	£-

[a] Based on commercial access agreement

Abbreviations: BSC, best supportive care; IO, immuno-oncology.

B.3.5.3.3 Treatment for patients in Distant Metastasis health state

3.5.3.3.1 Treatment costs for patients in DM health state

Treatment costs for patients in the DM1 health state were estimated based on the individual costs of the DM1 treatment options in the model, i.e., (i) Pembrolizumab alone (PD-L1≥50%), (ii) Pembrolizumab + chemotherapy (non-squamous histology), (iii) Pembrolizumab + chemotherapy (squamous histology), (iv) Chemotherapy (non-squamous histology), (v) Chemotherapy (squamous histology), (vi) BSC, (vii) Atezolizumab alone, and (vii) Atezolizumab + bevacizumab + chemotherapy (non-squamous histology).

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Similar to the LRR health state (described in Section B.3.5.3.1), the distribution of patients across the different treatment regimens was dependent on two pillars: 1) treatment at EF (IO or non-IO) and 2) IO retreatment restrictions, i.e., whether patients who received IO in EF and did not progress within a specific timeframe after completion of IO therapy are retreated with IO (i.e., pembrolizumab or atezolizumab with or without chemotherapy). Different distributions were calculated based on whether:

1. Patients received IO treatment in EF but retreatment is not permitted (e.g., because progression occurs within 6 months after the last dose of IO therapy). Patients cannot receive IO (pembrolizumab or atezolizumab with or without chemotherapy) in DM1. This is applicable for the perioperative durvalumab and neoadjuvant nivolumab + PDC treatment arms.

2. Patients have received IO treatment in EF and retreatment is permitted for those who have not progressed within 6 months after the last dose of IO therapy. These patients can receive IO (pembrolizumab or atezolizumab with or without chemotherapy) in DM1. This is applicable for the perioperative durvalumab and neoadjuvant nivolumab + PDC arms.

3. No IO treatment in EF; this is applicable for non-IO comparators, such as neoadjuvant PDC, adjuvant PDC, and surgery alone. These patients can receive IO (pembrolizumab or atezolizumab with or without chemotherapy) in DM1.

For DM1, the proportion of patients receiving BSC (i.e., 22.7%) in the model was informed by the percentage of patients receiving BSC following distant recurrence from Wong et al. 2016.[12] Based on TA683 and TA770 resource impact templates,[145,146] 80% of patients were assumed to receive active therapy, i.e., non-BSC. This means that 61.9% (i.e., 80% of 77.3%) received active therapy with IO (this relates to either patients who did not receive IO in EF or who received IO in EF but were retreated). To inform the distributions across the IO (pembrolizumab/atezolizumab) regimens, the AEGEAN population characteristics impacting subsequent therapy, such as PD-L1 ≥ 50% (for pembrolizumab/atezolizumab monotherapy), non-squamous (pembrolizumab/atezolizumab + cisplatin-based chemotherapy) and squamous histology (pembrolizumab + carboplatin-based chemotherapy) were considered. The distribution for patients receiving pembrolizumab versus atezolizumab in each setting was determined using IPSOS data.[147]The remainder of patients, i.e., those receiving treatment (but not active therapy with IO) were assigned to chemotherapy alone, based on the respective histology.

For patients not fulfilling the IO retreatment requirements, BSC based on Wong et al. 2016 (22.7%),[12] and chemotherapy (77.3%) based on the patients' histology were assigned.

Table 69 presents an overview of the distribution of treatment modalities for patients in the DM1 health state based on treatment received in EF.

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Table 69. 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)	17.5%	21.6%	15.7%	2.4%	4.7%	7.8%	7.6%	22.7%
No IO	17.5%	21.6%	15.7%	2.4%	4.7%	7.8%	7.6%	22.7%
Assumptions	IO+CT for patients receiving IO and PD-L1 <50% (based on IPSOS market shares for pembrolizumab/atezolizumab)	IO+CT for patients receiving IO 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 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 [12]

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

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For DM2, based on the SoC trials for metastatic NSCLC (i.e., KEYNOTE trials (pooled analysis across treatment arms)),[112,119-121] 44.6% of patients received BSC (regardless of treatment received in EF), and the remainder were treated with atezolizumab or docetaxel + nintedanib. Only patients who did not receive IO in DM1 could receive IO (i.e., atezolizumab) in DM2. The remaining patients received docetaxel + nintedanib. Patients receiving active treatment but who were not eligible for IO retreatment could only receive docetaxel + nintedanib. Table 70 shows the distributions of patients in DM2 by treatment modality.

Table 70. 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)	11.1%	44.3%	44.6%
No IO	11.1%	44.3%	44.6%
Assumptions	% BSC/no treatment for patients who received active treatment in DM1 based on 1% patients receiving subsequent therapy in KEYNOTE trials (5-year) (pooled across treatment arms)[112,119-121]		

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

B.3.5.3.4 Drug dose and unit costs for the DM health state

Drug dosing regimens per model cycle are presented in Table 71 and Table 72 for the DM1 and DM2 treatment modalities, respectively. Dose per treatment cycle was calculated based on the dose per administration, the number of administrations per treatment cycle, and the duration of the treatment cycle for each therapy, and then adjusted by the model cycle length.

Average dosages for intravenous interventions were calculated based on an BSA of 1.84 m^2 (as presented in Table 60). For the base case analysis, vial-sharing for intravenous chemotherapy was assumed to occur, therefore no wastage costs were included.

Table 71. Dosing regimen per cycle in DM1 health state

Treatment in DM health state	Dose per administration (mg)		Frequency (per treatment cycle) [a]	Max administrations	Source
Pembrolizumab	1500	mg	1	35	KEYNOTE-024 trial[119]
Pembrolizumab + Carboplatin + Pemetrexed	200	mg	1	35	KEYNOTE-189 trial[120]
	5	mg/ml/min	1	4	
	500	mg/m^2	1	35	
Carboplatin + Pemetrexed	5	mg/ml/min	1	4	
	500	mg/m^2	1	35	
Pembrolizumab + Carboplatin + Paclitaxel	200	mg	1	35	KEYNOTE-407 trial[121]
	6	mg/ml/min	1	4	
	200	mg/m^2	3	4	

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Carboplatin + Paclitaxel	6	mg/ml/min	1	4	
	200	mg/m^2	3	4	
Atezolizumab	1200	mg	1	Until PD or unmanageable toxicity	IMpower110[156]
Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel	1200	mg	1	Until PD or unmanageable toxicity	IMpower150[157]
	15	mg/kg	1		
	6	mg/ml/min	1	4	
	200	mg/m^2	3	4	

Abbreviations: DM, distant metastasis; PD, progressed disease.
[a] Treatment cycle length is 21 days.

Table 72. Dosing regimen per cycle in DM2 health state

Treatment in DM health state	Dose per administration (mg)		Frequency (per treatment cycle)	Max administrations	Source
Atezolizumab	1200	mg	1	Until PD or unmanageable toxicity	OAK trial[158]
Docetaxel + Nintedanib	137.8	mg/m^2	1	Until PD or unmanageable toxicity	LUME-Lung 1[159]
	200	mg	42	Until PD or unmanageable toxicity	

Abbreviations: DM, distant metastasis; PD, progressed disease.
[a] Treatment cycle length is 21 days.

Unit acquisition costs relevant to the DM (DM1 and DM2) health state were sourced from the BNF and eMIT databases and presented in Table 73.

Table 73. Unit acquisition costs for the components of the DM health state treatment options

Treatment	Dose per vial/tablet (mg)	Cost per pack	Cost per mg	Source
Pembrolizumab	100	£2,630.00	£26.30	*BNF 2023 (via NICE)[153]*
Atezolizumab	840	£2,665.38	£3.17	*BNF 2023 (via NICE)[153]*
	1200	£3,807.69	£3.17	*BNF 2023 (via NICE)[153]*
Bevacizumab	100	£205.55	£2.06	*BNF 2023 (via NICE)[153]*
	400	£810.10	£2.03	*BNF 2023 (via NICE)[153]*
Nintedanib	100	£2,151.00	£0.36	*BNF 2023 (via NICE)[153]*
	150	£2,151.00	£0.24	*BNF 2023 (via NICE)[153]*
	100	£2,151.00	£0.18	*BNF 2023 (via NICE)[153]*
Carboplatin	150	£7.44	£0.08	*eMIT NPC code DHE001[85]*
	450	£14.69	£0.04	*eMIT NPC code DHE002[85]*
	50	£4.05	£0.10	*eMIT NPC code DHE003[85]*
	600	£21.54	£0.24	*eMIT NPC code DHE162[85]*
Cisplatin	100	£9.53	£0.11	*eMIT NPC code DHA010[85]*
	10	£2.42	£0.18	*eMIT NPC code DHA013[85]*
	50	£5.58	£0.10	*eMIT NPC code DHA011[85]*
Docetaxel	20	£3.68	£0.10	*eMIT NPC code DHC025[85]*
	80	£8.17	£0.03	*eMIT NPC code DHC029[85]*
	160	£16.04	£0.02	*eMIT NPC code DHC046[85]*
Paclitaxel	100	£11.49	£0.11	*eMIT NPC code DHA145[85]*
	150	£17.28	£0.12	*eMIT NPC code DHA297[85]*

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Treatment	Dose per vial/tablet (mg)	Cost per pack	Cost per mg	Source
	300	£17.40	£0.06	*eMIT NPC code DHA210*[85]
	30	£4.03	£0.13	*eMIT NPC code DHA144*[85]
Pemetrexed	100	£29.11	£0.29	*eMIT NPC code DYC062*[85]
	500	£45.70	£0.09	*eMIT NPC code DYC063*[85]
	850	£49.93	£0.06	*eMIT NPC code DZV051*[85]
	1000	£81.30	£0.08	*eMIT NPC code DEI018*[85]
No treatment/BSC	N/A	£0.00	£0.00	N/A

Abbreviations: BNF, British National Formulary; BSC, best supportive care; eMIT, electronic market information tool.

The same approach used for the LRR health state was followed for the calculation of DM1 treatment-related costs. A treatment basket containing the individual components of the DM1 treatment combinations was defined, and durations, proportions and costs were calculated separately. Of note, as per LRR, these proportions are cumulative across treatments, and therefore do not sum to 100%.

Table 74 presents an overview of the treatment durations, proportion receiving each treatment from the treatment basket, and associated treatment acquisition and administration costs relevant for the DM1 health state.

Table 74. Overview of treatment duration, costs and proportion of patients receiving DM1 treatments from a treatment basket

Treatment basket	Duration (model cycle)	Proportion of patients receiving:		Treatment costs per cycle	Admin costs per cycle
		No IO retreatment	IO retreatment		
Pembrolizumab	24.1	0.0%	54.7%	£7,623.87	£207.59
Carboplatin (nsq) (comb. Pembrolizumab)	2.8	0.0%	17.5%	£26.84	£- [a]
Carboplatin (nsq)	2.8	39.2%	7.8%	£26.84	£440.71
Carboplatin (sq) (comb. Pembrolizumab)	2.8	0.0%	21.6%	£32.21	£- [a]
Carboplatin (sq)	2.8	38.1%	7.6%	£32.21	£440.71
Pemetrexed	24.1	39.2%	25.3%	£74.01	£- [a]
Paclitaxel	2.8	38.1%	29.2%	£151.57	£652.92
BSC	0.0	22.7%	22.7%	£-	£- [a]
Atezolizumab	432.0	0.0%	7.1%	£5,518.88	£207.59
Bevacizumab	432.0	0.0%	4.7%	£3,147.83	£- [a]
Paclitaxel (nsq)	2.8	0.0%	4.7%	£92.67	£652.92

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Abbreviations: BSC, best supportive care; CT, chemotherapy; DM, distant metastasis IO, immuno-oncology; nsq, non-squamous; sq, squamous.
[a] Administration costs have been accounted for the treatment combination

To estimate the treatment costs associated with the DM2 health state, given that all DM2 options were monotherapies, a treatment basket approach was not required. Thus, costs per treatment were calculated per treatment modality, and are presented in Table 75.

Table 75. Overview of treatment duration, costs in the DM2 health state

Treatment basket	Duration (model cycle)	Proportion of patients receiving:		Treatment costs per cycle	Admin costs per cycle
		No IO retreatment	IO retreatment		
Atezolizumab	432.0	0.0%	11.1%	£5,518.88	£207.59
Docetaxel + Nintedanib	432.0	55.4%	44.3%	£2,202.39	£207.59
BSC	0.0	22.7%	22.7%	£-	£-

Abbreviations: BSC, best supportive care; DM, distant metastasis IO, immuno-oncology.

B.3.5.4 *Treatment monitoring costs*

Regular biochemistry and haematology testing costs, sourced from NHS Reference costs 2021/2022,[154] were applied in each model cycle to all patients receiving treatment. For the requirements during EF, one test per treatment cycle was assumed based on KOL validation in TA876.[50] Since treatment labels didn't specify test frequencies, it was assumed each test was performed once per treatment cycle, in line with TA876 (Table 76).[50]

Table 76. Monitoring costs

Health state	Test	Unit cost	Cost per treatment cycle	Source
EF	Liver function test	£1.55	£2.25	NHS Reference Costs 2021/2022, DAPS04 - Clinical biochemistry[154]
Other health states			£8.99	
EF	Renal function test	£1.55	£2.25	NHS Reference Costs 2021/2022, DAPS04 - Clinical biochemistry[154]
Other health states			£8.99	
EF	Complete blood count	£2.96	£4.29	NHS Reference Costs 2021/2022, DAPS05 - Haematology[154]
Other health states			£17.17	

Abbreviations: EF, event-free.

B.3.5.5 *Healthcare resource use and costs*

HCRU data relating to clinical visits, hospitalisation, and imaging for each of the model health states were sourced from the LuCaBIS study by Andreas et al., 2018[14], in line with the HCRU data presented in TA761.[59] The study evaluated resource use and costs associated

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with managing patients with resected stage IB–IIIA NSCLC during and after adjuvant therapy, and after disease progression to LRR or DM health states, in three European countries. The UK-specific data for each health state were adjusted by the time spent in each state to calculate the average resource use per model cycle (see Table 77). Unit costs for HCRU were sourced from NHS Reference costs 2021/2022[154] and are presented in Table 78. A summary of the total health state costs per cycle is provided in Table 79.

Table 77. Healthcare resource use by health state

Resource items	Frequency (per model cycle)			
	EF (neoadjuvant /adjuvant)	LRR	DM1	DM2
PET scans	0.050	0.100	0.250	0.250
PET-CT scans	0.071	0.100	0.125	0.125
CT scans	0.086	0.220	0.287	0.287
MRI	0.048	0.100	0.150	0.150
Ultrasound	0.075	0.100	0.162	0.162
Nuclear medicine studies	0.023	0.100	0.125	0.125
Accident & Emergency	0.071	0.130	0.175	0.175
Surgeon visits	0.164	0.200	0.162	0.162
Oncology visits	0.093	0.690	0.662	0.662
Pulmonologist/respiratory physician	0.166	0.260	0.125	0.125
Hospitalisation	0.075	0.130	0.225	0.225
Other specialist visit	0.159	0.250	0.162	0.162

Abbreviations: CT, computed tomography, EF, event-free; DM, distant metastasis; LRR, locoregional recurrence; MRI, magnetic resonance imaging; PD, progressed disease; PET, positron emission tomography; PF, progression-free.

Table 78. Healthcare resource unit costs

Resources required	Unit cost	Source: NHS Reference costs 2021/2022[154]
PET scans	£665.48	RN07A - Positron Emission Tomography (PET), 19 years and over
PET-CT scans	£631.46	RN01A/RN02A/RN03A - Positron Emission Tomography with Computed Tomography (PETCT) of One/Two or Three/more than Three Area, 19 years and over (weighted average)
CT scans	£142.47	RD24Z - Computerised Tomography Scan of two areas, with contrast
MRI	£243.18	HRG code RD05Z - Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
Ultrasound	£82.35	RD41Z/RD43Z - Ultrasound Scan with duration of less than 20 minutes/20 minutes and over, with Contrast (weighted average)
Nuclear medicine studies	£219.50	NHS Reference costs 2021/2022 - WF01B/WF01A, Nuclear medicine, non-admitted face-to-face attendance, first and follow-up (weighted average)
Accident & Emergency	£278.10	AE, VB01Z-09Z, Emergency department visit, elective inpatient (weighted average)
Surgeon visits	£244.29	173 WF01A - Thoracic Surgery consultant led outpatient attendance

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Oncology visits	£221.48	370 WF01A - Medical oncology service, non-admitted face-to-face attendance, follow-up, consultant led
Pulmonologist/respiratory physician	£827.12	340 WF01A - Respiratory medicine, non-admitted face-to-face attendance, follow-up, consultant led
Hospitalisation	£2,217.42	DZ19H-N - Other Respiratory Disorders with/without Single/Multiple Interventions, with CC Score 0-11+; Non-elective long and short stay (weighted average)
Other specialist visit	£221.48	WF01A - Medical oncology service, non-admitted face-to-face attendance, follow-up, consultant led

Abbreviations: CT, computed tomography; DFS, disease-free survival; MRI, magnetic resonance imaging; NHS, National Health Service; PET, positron emission tomography.

Table 79. Total healthcare resource use per health state cycle

Health state	Cost per cycle
EF (neoadjuvant/adjuvant)	£532.44
LRR	£992.81
PF with DM	£1,235.84
PD with DM	£1,235.84

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

A one-time terminal care cost was applied to all patients in the model upon transition to the death state to capture healthcare costs at the end of life (see Table 80). The terminal care cost was calculated based on the proportion of patients who received end of life care in hospital, in a hospice, or at home, sourced from Brown et al.[160] Cost inputs were sourced from NHS Reference costs 2021/2022,[154] the PSSRU 2019,[161] and a Marie Curie report.[162]

Table 80. Terminal care cost

Terminal care setting	Patients that died per setting (%)	Unit cost	Source
Hospital	55.8	£2,878.29	Distribution of patients: Brown et al.[160], Costs: NICE TA761; NHS Reference Costs 2021/2022 DZ17L-V Respiratory Neoplasms with/without Single/Multiple Interventions, with CC Score 0-13+; Non-elective long and short stay (weighted average)
Hospice	16.9	£3,597.86	Distribution of patients: Brown et al.[160], Costs: Assuming 25% increase on hospital inpatients care (as per TA761)
Home	27.3	£2,183.87	Distribution of patients: Brown et al.[160], Costs: NICE TA761; 28 hours community nurse visit including travel time: N02AF - District Nurse, Adult, Face to face (NHS Reference Costs 2021/2022; £54.74 per hour) 7 GP home visits excluding travel time: Per patient contact lasting 9.22 minutes (incl. qualification and direct staff costs) (PSSRU 2022; £42) Drugs and equipment - Marie Curie report figure of £240 (2003/04) updated to 2021/2022 value using HCHS and NHSCII from PSSRU 2010 and 2022
Total	£2,810.32		

Abbreviations: GP, general practitioner; HCHS, Hospital and Community Health Service; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; NHSCII, National Health Service Cost Inflation Index; PSSRU, Personal Social Services Research Unit; TA, technology appraisal

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B.3.5.6 *Adverse reaction unit costs and resource use*

Costs for grade 3 or 4 AEs occurring in more than 5% of patients during the neoadjuvant or adjuvant treatment phases in the AEGEAN trial were considered in the cost effectiveness analyses. For perioperative durvalumab and neoadjuvant PDC, AE frequencies were obtained from the AEGEAN trial (EFS IA1 [DCO 10 November 2022]). For neoadjuvant nivolumab + PDC, surgery alone and adjuvant PDC,AE frequencies were extracted from publicly available sources (see Table 81). The duration of each AE was assumed to be one month for all AEs irrespective of therapy. The costs of managing AEs were sourced from the NHS Reference Costs 2021/2022[154] as a weighted average of total treatment costs for each AE considered (see Table 82). The AE costs and decrement in HRQoL (i.e., disutility related to AEs) were applied as a one-off cost/disutility in the first cycle of the model.

Table 81. Treatment-emergent grade 3/4 adverse event frequencies

Adverse event	Perioperative durvalumab	Neoadjuvant PDC	Neoadjuvant nivolumab + PDC	Surgery alone	Adjuvant PDC
Neutropenia	9%	9%	9%	0%	9%
Neutrophil count decreased	10%	11%	7%	0%	11%
Anaemia	5%	5%	3%	0%	5%
Source	AEGEAN[20]	AEGEAN[20]	CM816[66]	Surgery-related AEs of Grade 3-4 assumed to be 0% (as per TA876 - CM816)[50,66]	Assumed to be same as neoadjuvant PDC

Abbreviations: AE, adverse event; CRT, chemoradiotherapy; PDC, platinum doublet chemotherapy; RT, radiotherapy; TA, technology appraisal.

Table 82. Adverse event unit costs

Adverse event	Unit cost	Source
Neutropenia	£ 1365.50	National Schedule of NHS Costs 2021/2022 - Weighted average of total costs for: SA08G-J[154]
Neutrophil count decreased	£ 1365.50	Assumed to be the same as for neutropenia
Anaemia	£ 537.43	National Schedule of NHS Costs 2021/2022 - Weighted average of total costs for: SA04G-L[154]

Abbreviations: NHS, National Health Service.

B.3.6 *Managed access proposal*

This submission proposes perioperative durvalumab is commissioned for routine use in patients within its expected licensed population based on the robust clinical evidence provided by the AEGEAN trial; however, it may become relevant for perioperative durvalumab to be considered as a candidate for the Cancer Drugs Fund (CDF) under a managed access agreement, if areas of clinical uncertainty are identified during the appraisal process.

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B.3.7 *Summary of base-case analysis inputs and assumptions*

B.3.7.1 *Summary of base-case analysis inputs*

An overview of the key variables applied in the base-case analysis are presented in Table 83, alongside the justification for the setting and corresponding reference in the submission document.

Table 83. Summary of key variables applied in the economic model

Variable	Value	Justification	Reference to section in submission
Model settings			
Perspective	Payer	NICE reference case[163]	B.3.2
Time horizon	36 years	NICE reference case[163]	B.3.2
Cycle length	4.35 weeks	NICE reference case[163]	B.3.2
Discount rate for costs	3.5%	NICE reference case[163]	B.3.2
Discount rate for benefits	3.5%	NICE reference case[163]	B.3.2
Population characteristics			
Patients' age at baseline (mean)	64 years	AEGEAN[20]	B.2.3.3
Percentage male	71.6%	AEGEAN[20]	B.2.3.3
Patients' average weight	[redacted]	AEGEAN[20]	B.3.5.2
Patients' average weight	[redacted]	AEGEAN[20]	B.3.5.2
BSA	[redacted]	As per AEGEAN population combined with Gehan and George formula[20,152]	B.3.5.2
Clinical inputs			
EFS Parametric modelling	Log-normal	Appropriate fit in terms of AIC/BIC, validated with clinical experts[22] and against external sources[64]	B.3.3.3
Transition from EF to LRR	Assumed to account for [redacted] of the non-death EFS events	Based on KOL feedback[22]	B.3.3.3.1
Transition from EF to DM	Assumed to account for [redacted] of the non-death EFS events	Based on KOL feedback[22]	B.3.3.3.1
Mortality in EFS	Log-normal	Consistency with parametric modelling of EFS	B.3.3.3.2

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Variable	Value	Justification	Reference to section in submission
TTP from PACIFIC informing the transition from LRR to DM	Generalised Gamma	Base case as per TA798 (PACIFIC)[127]	B.3.3.4.1
PFS from PACIFIC informing the transition from LRR to death	Generalised Gamma	Base case as per TA798 (PACIFIC) [127]	B.3.3.4.2
OS after LRR from Wong et al. 2016 informing the transition from LRR to death	Log-normal	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.4.2
KEYNOTE-024 PFS (Pembro arm) informing the transition from DM to death	Log-logistic	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.5
KEYNOTE-189 PFS (Pembro + CT arm) informing the transition from DM to death	Log-normal	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.5
KEYNOTE-407 PFS (Pembro + CT arm) informing the transition from DM to death	Log-logistic	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.5
KEYNOTE-189 PFS (Placebo + CT arm) informing the transition from DM to death	Log-normal	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.5
KEYNOTE-407 PFS (Placebo + CT arm) informing the transition from DM to death	Log-logistic	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.5
KEYNOTE-024 OS (Pembro arm) informing the transition from DM to death	Log-normal	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.5
KEYNOTE-189 OS (Pembro + CT arm) informing the transition from DM to death	Log-logistic	Best fit in terms of AIC/BIC given the maturity of the data, also used as base case for OS in TA683[123]	B.3.3.5
KEYNOTE-407 OS (Pembro + CT arm) informing the transition from DM to death	Log-logistic	Best fit in terms of AIC/BIC given the maturity of the data, also used as base case for OS in TA770[128]	B.3.3.5
KEYNOTE-189 OS (Placebo + CT arm) informing the transition from DM to death	Log-logistic	Best fit in terms of AIC/BIC given the maturity of the data, also used as base case for OS in TA683[123]	B.3.3.5

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Variable	Value	Justification	Reference to section in submission
KEYNOTE-407 OS (Placebo + CT arm) informing the transition from DM to death	Log-logistic	Best fit in terms of AIC/BIC given the maturity of the data, also used as base case for OS in TA770[128]	B.3.3.5
OS after DM from Wong et al. 2016 informing the transition from DM to death	Log-normal	Best fit in terms of AIC/BIC given the maturity of the data	B.3.3.5
Cure assumption	Yes	Based on literature, KOL feedback and previous NICE submissions (TA761, TA823, TA876) supporting the use of cure assumptions[23,50,59]	B.3.3.3.3
Onset of cure	5 years	Based on KOL feedback[22]	B.3.3.3.3
Warm up period from start to cure timepoint	0 years	Assumptions	B.3.3.3.3
% cured	95%	Based on KOL feedback[22]	B.3.3.3.3
IO retreatment timepoint	6 months after completion of IO therapy (neoadjuvant or adjuvant)	Based on TA823, where the NHS England representative stated that retreatment with IO is likely to happened after 6 months to 1 year after IO treatment, if patients had not progressed within initial IO.[23] Also in line with TA876[50] and validated by UK clinicians.[22]	B.3.2
Cost inputs			
Duration of neoadjuvant treatment	4 cycles for the AEGEAN comparators; 3 cycles for neoadjuvant nivolumab + PDC	Based on the relevant clinical trials	B.3.5.2.1
Duration of adjuvant treatment	12 cycles for the AEGEAN comparators; 4 cycles for adjuvant PDC and neoadjuvant nivolumab + PDC comparators	Based on the relevant clinical trials	B.3.5.2.1
MRU frequency and costs	Based on LuCaBIS study	Study identified in the SLR, suitable for the patient population and previously used in NICE	B.3.5.5

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Variable	Value	Justification	Reference to section in submission
		submissions in the same indication (e.g., TA761, TA876)[50,59]	
Utilities			
Baseline utility	0.829	UK general population utility based on the HSE 2014 dataset for the AEGEAN age at baseline[150]	B.3.4.5
Utility EF	[redacted]	Based on data collected in AEGEAN using UK weights[122]	B.3.4.3
Utility LRR	[redacted]	Based on utility value derived from PACIFIC, reported in TA798[127]	B.3.4.3
Utility: DM1 (pre-progression)	0.759	Based on the pre-progression utility value from KEYNOTE-189, reported in TA683 (SoC appraisal in mNSCLC)[123]	B.3.4.3
Utility: DM2 (post-progression)	0.662	Based on the post-progression utility value from KEYNOTE-189, reported in TA683 (SoC appraisal in mNSCLC) [123]	B.3.4.3
Disutilities due to AEs	Neutropenia: -0.007 Neutrophil count decreased: -0.007 Anaemia: -0.007	In line with Nafees et al. 2008 and TA876[50,149]	B.3.4.4

Abbreviations: Abbreviations: AE, adverse event; AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; EFS, event-free survival; DM1, distant metastasis pre-progression; DM2, distant metastasis post-progression; KOL, Key opinion leader; LRR, locoregional recurrence; NHS, National Health Service; NICE, National Institute of Health and Care Excellence; SLR, systematic literature review; QoL, quality of life; TA, technology appraisal; UK, United Kingdom

Sources: cited in table

B.3.7.2 *Assumptions*

Table 84 summarises the key assumptions used in the economic model.

Table 84. Summary of key assumptions used in the economic model

Assumption	Rationale
The AEGEAN trial population was assumed to be representative of patients receiving treatment for stage IIA-IIB resectable NSCLC.	This is a necessary limitation of a cohort-level approach.

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Assumption	Rationale
A lifetime (36 years) time horizon was used.	To align with the NICE reference case[116] for the patient population and capture all the costs and benefits from perioperative durvalumab over a lifetime horizon (<1% of the patients in the durvalumab arm remain alive at 36 years in the analysis).
Survival outcomes from the AEGEAN trial were extrapolated with an assumption of patients transitioning to cured if they remained in the EF state, assuming a 5-year cure timepoint.	To reflect the expected clinical outcomes using AEGEAN data (from the first interim analysis), a 5-year cure timepoint was applied, taking into account the expectation of a plateau towards the 5-year mark: event-free patients are typically discharged and not followed by clinicians after 5 years, and therefore are considered to be functionally cured. This assumption was validated by clinical experts.[22] The cure assumption is also consistent with the preferred approach describe in previous NICE appraisals in adjuvant, early-stage cancer.[106,124] The model assumed that 95% of patients would be cured if they had remained in the EF health state at 5 years. This is consistent with the preferred approach described in NICE technology appraisals in adjuvant, early-stage cancer (TA569, TA642, TA761, TA876).[50,59,106,124]
IO retreatment restrictions	In the appraisal committee meeting feedback on TA823,[23] the NHS England representative argued that retreatment with IO in recurrence after receiving IO in the adjuvant setting would be expected. In line with TA876,[50] UK clinical practice[139] and validated by UK clinical experts, it was assumed that retreatment with IO at LRR and DM would be allowed for patients who have not progressed after 6 months of completion of IO in the neoadjuvant/ adjuvant phase (in the EF health state).[22]
Patient transition from EF to LRR and DM health states	Clinical experts validated the proportion of patients in the EF state who transition to LRR and those who transition to the DM health state in a UK advisory board.[22] The same proportions were assumed across both arms in line with TA823,[23] and across all comparators This assumption was validated by clinical experts.[22] Alternative proportions for the transitions to LRR and DM were tested in scenario analysis.
No subsequent metastasis for patients receiving BSC in LRR but patients were assumed to be transitioning directly to the dead state	According to TA823, it was assumed that patients in BSC can only transition from LRR to death, given that they will not receive any further treatment.[23] The efficacy was informed by the Wong et al. 2016 study based on OS after LRR.[12]
Treatment in LRR and DM1	The proportion of patients receiving subsequent therapies in LRR and DM1 is dependent on the treatments received in EF, population characteristics impacting subsequent therapy (e.g., PD-L1 status, non-squamous, squamous histology) and IO retreatment eligibility settings based on the NICE TA798 and TA770 resource impact templates.[30,145,146]
Transition from LRR to death for Months 1 and 2 receiving treatment	For patients transitioning from LRR to death in the first two model cycles, GPM was assumed.[131]

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Assumption	Rationale
Treatment in DM2	The proportion of patients receiving subsequent therapies in DM2 was dependent on the treatments received in EF and DM1. • The proportion of patients receiving BSC was informed by the pooled analysis of the KEYNOTE-024, KEYNOTE-189 and KEYNOTE-407 trials.[119-121] • Patients can receive active treatments (i.e., atezolizumab, docetaxel + nintedanib).
Survival was limited by general population mortality	All parametric distributions were limited by the general population mortality in the UK. This assumed that modelled patients did not achieve better mortality outcomes than the general UK population.[131]
In the surgery alone arm, all patients were assumed to receive surgery.	This assumption was considered for logical consistency.
In the adjuvant PDC arm, all patients were assumed to receive adjuvant treatment	This assumption was considered for logical consistency.
Utility values across treatments	The health state utility values were assumed to be equivalent across treatments (i.e., utilities are not treatment-specific).
Utility values in the LRR and DM health states	The health state utility for LRR was based on TA798 which used EQ-5D from PACIFIC.[127] The health state utility values for DM health states were adopted from TA683, based on the EQ-5D scores for pre-progression and post-progression in mNSCLC from KEYNOTE-189 (study used to inform post-recurrence outcomes).[123] The utility values were also validated by clinical experts.[22]
Vial sharing	In line with NHS practice, vial sharing was assumed for chemotherapy costs, as hospitals are expected to optimise treatments administered on the same day. However, a scenario with no vial sharing, i.e., inclusion of wastage costs is included in the model.
Treatment discontinuation at EF based on the AEGEAN TDT data across all comparators	The AEGEAN TDT data for perioperative durvalumab and neoadjuvant PDC in the two AEGEAN arms were separately used to inform the TDT for all non-AEGEAN comparator arms. This was done to replicate both the treatment setting (neoadjuvant/adjuvant) and the treatment type. Specifically, the IO treatment mirrored the AEGEAN perioperative durvalumab TDT data, while the chemotherapy treatment mirrored the neoadjuvant PDC TDT data.
AE duration	The duration of AEs were assumed to extend for up to one month across all treatments in the model.
Terminal care costs	In line with TA761, it was assumed terminal care in hospice will lead to an increase of 25% in costs, compared to care in a hospital.[59]

Abbreviations: AE, adverse event; EF, event-free; DM1, distant metastasis pre-progression; DM2, distant metastasis post-progression; LRR, locoregional recurrence; NHS, National Health Service; QoL, quality of life.

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B.3.8 *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 B.3.9.

B.3.8.1 *Base-case incremental cost-effectiveness analysis deterministic results*

The deterministic base case results are presented in Table 85 to Table 88. These results are based on the current commercial access agreement for durvalumab as presented in Table 61. Per NICE guidelines the results are presented as pairwise comparisons given that perioperative durvalumab is expected to replace the individual comparator therapies.

Table 89 presents the incremental deterministic net health benefit (NHB) per treatment versus perioperative durvalumab.[164]

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Table 85. 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]	£4,708

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

Table 86. 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]	£19,575

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

Table 87. 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 88. 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]	£4,458

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

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Table 89. 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]	1.35	1.49
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	0.02	0.26
Surgery alone	[redacted]	[redacted]	2.91	2.84
Adjuvant PDC	[redacted]	[redacted]	1.42	1.56

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

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B.3.8.2 *Clinical outcomes from the model*

Clinical outcomes from the model are presented in detail in Appendix J.

B.3.9 *Exploring uncertainty*

B.3.9.1 *Base-case incremental cost-effectiveness analysis probabilistic results*

B.3.9.1.1 Probabilistic sensitivity analysis

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. Additional details regarding the PSA are provided in Appendix O.

B.3.9.1.2 PSA results

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 90 to Table 92. These results are based on the confidential commercial access agreement for durvalumab as presented in Table 61. 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 93.

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Table 90. 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]	£6,194

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

Table 91. 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]	£23,625

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

Table . 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 92. 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]	£4,872

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

Table 93. 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]	1.16	1.33
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	-0.12	0.14
Surgery alone	[redacted]	[redacted]	2.72	2.69
Adjuvant PDC	[redacted]	[redacted]	1.36	1.50

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Abbreviations: CRT, chemoradiotherapy; 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 38 to Figure 41 and Figure 42 to Figure 45, respectively.

Figure 38. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant PDC

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

Figure 39. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant nivolumab + PDC

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

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Figure 40. Incremental cost effectiveness plane: perioperative durvalumab versus surgery alone

Abbreviations: QALY, quality-adjusted life year

Figure 41. Incremental cost effectiveness plane: perioperative durvalumab versus adjuvant PDC

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

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Figure 42. CEAC: perioperative durvalumab versus neoadjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy

Figure 43. CEAC: perioperative durvalumab versus neoadjuvant nivolumab + PDC

Abbreviations: PDC, platinum-doublet chemotherapy

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Figure 44. CEAC: perioperative durvalumab versus surgery alone

Figure 45. CEAC: perioperative durvalumab versus adjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy

B.3.9.2 *Deterministic sensitivity analysis*

All major model variables in the base case were tested in OWSA to identify key model drivers and examine key areas of uncertainty. The base case inputs for the majority of parameters were varied using the 95% confidence intervals where available. In the absence of 95% confidence intervals, upper and lower bounds utilised in the OWSA were calculated assuming a standard error of 0.1.

The results from the OWSA are presented in a tornado diagram for each pairwise comparison in Figure 46 to Figure 49. 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 (please refer to Appendix P for the exact ICERs). This is to enable a clearer understanding of the impact of the other parameters.

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As expected, the key drivers of cost-effectiveness were the EFS HR versus neoadjuvant PDC, the discount rates for health benefits and costs, as well as the time period from last dose of neoadjuvant therapy to receiving adjuvant therapy. Additional information regarding the key parameters with the greatest impact and their estimated ICERs can be found in Appendix P.

Figure 46. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence

Figure 47. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant nivolumab + PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence

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Figure 48. Tornado diagram from OWSA - perioperative durvalumab vs. surgery alone

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence

Figure 49. Tornado diagram from OWSA - perioperative durvalumab vs. adjuvant PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; TP, transition probability

B.3.9.3 *Scenario analysis*

Scenario analysis was conducted by running the probabilistic analysis for 1,000 iterations. Table 94 presents an overview and justification for each scenario.

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Table 95 to Table 98 present the scenario analyses results for each comparator.

There was a minor impact on the model outcomes compared to the base-case ICER (less than 10% difference) for the majority of the scenarios, and results remained within or below the £20,000 - £30,000 per QALY range. The scenario with the greatest impact across all comparators, was the EFS HR when applied to standard extrapolations. This resulted in ICERs of £2,391, £9,752 and £35 for perioperative durvalumab versus neoadjuvant PDC, neoadjuvant nivolumab + PDC, and adjuvant PDC, accordingly. Durvalumab is dominant versus surgery alone.

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Table 94. 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[50]
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	38.8%	61.2%	Testing the impact of applying site of recurrence data from AEGEAN, pooled data across arms
3	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
4	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
5	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[50]
6	EFS HR: applied to standard extrapolations	Piecewise extrapolation	Standard extrapolation	Test the impact of applying a single HR over time, instead of only post-surgery
7	No IO re-treatment permitted	6	481	Testing an extreme scenario whereby retreatment is not permitted.
8	EF utility capped at UK general population norm	0.838	0.829	EF utility from the AEGEAN EQ-5D utility analysis is slightly higher than that of the UK general population, so testing the impact of using the latter.
9	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).[14,59]
10	Discounting costs/effects: 1.5%	3.5%	1.5%	Exploring the impact of a lower discount rate for cost or health effects (extreme scenario)

Abbreviations: CRT, chemoradiotherapy; 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

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Table 95. Scenario analyses results perioperative durvalumab versus neoadjuvant PDC

Scenario nr.	Scenario label	Perioperative durvalumab vs. neoadjuvant PDC			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
N/A	Base case	[redacted]	[redacted]	£4,708	-
1	Apply a warm-up period of 12 months starting from year 5	[redacted]	[redacted]	£4,531	-3.8%
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	£5,493	16.7%
3	EFS distribution for neoadjuvant PDC arm: loglogistic	[redacted]	[redacted]	£3,719	-21.0%
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	£4,778	1.5%
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	£2,747	-41.7%
6	EFS HR: applied to standard extrapolations	[redacted]	[redacted]	£2,391	-49.2%
7	No IO re-treatment permitted	[redacted]	[redacted]	£3,826	-18.7%
8	EF utility capped at UK general population norm	[redacted]	[redacted]	£4,779	1.5%
9	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	£5,840	24.0%
10	Discounting costs/effects: 1.5%	[redacted]	[redacted]	£4,531	-3.8%

Abbreviations: CRT, chemoradiotherapy; 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 96. 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]	£19,575	-
1	Apply a warm-up period of 12 months starting from year 5	[redacted]	[redacted]	£19,210	-1.9%
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	£19,527	-0.2%
3	EFS distribution for neoadjuvant PDC arm: loglogistic	[redacted]	[redacted]	£17,729	-9.4%

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Scenario nr.	Scenario label	Perioperative durvalumab vs. neoadjuvant nivolumab + PDC			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	£16,884	-13.7%
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	£14,759	-24.6%
6	EFS HR: applied to standard extrapolations	[redacted]	[redacted]	£9,752	-50.2%
7	No IO re-treatment permitted	[redacted]	[redacted]	£28,250	44.3%
8	EF utility capped at UK general population norm	[redacted]	[redacted]	£19,859	1.4%
9	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	£24,084	23.0%
10	Discounting costs/effects: 1.5%	[redacted]	[redacted]	£14,478	-26.0%

Abbreviations: CRT, chemoradiotherapy; 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 97. Scenario analyses results perioperative durvalumab versus surgery alone

Scenario nr.	Scenario label	Perioperative durvalumab vs. surgery alone			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
N/A	Base case	[redacted]	[redacted]	Dominant	-
1	Apply a warm-up period of 12 months starting from year 5	[redacted]	[redacted]	Dominant	-
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	Dominant	-
3	EFS distribution for neoadjuvant PDC arm: loglogistic	[redacted]	[redacted]	Dominant	-
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	Dominant	-
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	Dominant	-
6	EFS HR: applied to standard extrapolations	[redacted]	[redacted]	Dominant	-
7	No IO re-treatment permitted	[redacted]	[redacted]	Dominant	-
8	EF utility capped at UK general population norm	[redacted]	[redacted]	Dominant	-
9	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	Dominant	-

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Scenario nr.	Scenario label	Perioperative durvalumab vs. surgery alone			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
10	Discounting costs/effects: 1.5%	[redacted]	[redacted]	Dominant	-

Abbreviations: CRT, chemoradiotherapy; 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 98. Scenario analyses results perioperative durvalumab versus adjuvant PDC

Scenario nr.	Scenario label	Perioperative durvalumab vs. adjuvant PDC			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
N/A	Base case	[redacted]	[redacted]	£4,458	-
1	Apply a warm-up period of 12 months starting from year 5	[redacted]	[redacted]	£4,320	-3.1%
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	£5,077	13.9%
3	EFS distribution for neoadjuvant PDC arm: loglogistic	[redacted]	[redacted]	£3,539	-20.6%
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	£4,755	6.7%
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	£2,718	-39.0%
6	EFS HR: applied to standard extrapolations	[redacted]	[redacted]	£35	-99.2%
7	No IO re-treatment permitted	[redacted]	[redacted]	£3,604	-19.2%
8	EF utility capped at UK general population norm	[redacted]	[redacted]	£4,525	1.5%
9	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	£5,528	24.0%
10	Discounting costs/effects: 1.5%	[redacted]	[redacted]	£2,241	-49.7%

Abbreviations: CRT, chemoradiotherapy; 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

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B.3.10 *Benefits not captured in the QALY calculation*

The model captures benefits related to the QoL of patients over a lifetime, as well as decrements related to AEs. However, there are wider benefits in the treatment with a new intervention that the QALY calculation has not accounted for. For example, health benefits for the patients may be translated to society benefits, if a patient's health is improved enough for them to return to work. In addition, improvements in patients' health may also lead to reduced requirements for informal caregiving.[165] Some of these aspects can be captured in the analysis, however it is not always possible to capture all benefits with a single index.[166]

B.3.11 *Subgroup analysis*

No relevant subgroup analyses were performed.

B.3.12 *Validation*

B.3.12.1 *Validation of cost-effectiveness analysis*

B.3.12.1.1 Technical validation by model developer

A health economist formally validated the cost-effectiveness analysis for internal accuracy. This included checking technical design, calculation implementation, formula accuracy, and extreme value testing. Distributions in the probabilistic analysis were examined, and model structure and inputs were compared with previous NICE appraisals. The methodology described throughout this submission followed the NICE guide for health technology evaluations (2022).[163] Validation used a checklist aligned with detailed checklists for thoroughness.[167] Errors identified during validation were corrected and integrated into the model.

B.3.12.1.2 Third-party validation

Following the internal validation by the model developer, the model was also validated by another Health Economics and Outcomes Research (HEOR) consultancy. This validation was undertaken by experienced HEOR modelling experts in January 2024. This second round of validation mainly focused on ensuring the model's conceptual validity regarding the model structure, logic, mathematical, and causal relationships at the conceptual level. In addition, the validation assessed the internal technical validity of the model ensuring that the programming of the conceptual model has been conducted appropriately.

This validation also included extreme value testing analysis, and directional input testing, where input parameters are modified individually and their directional relationship with cost and QALY outcomes are evaluated. This approach is in line with established Good Model Validation Practice guidance as presented by ISPOR,[168] NICE,[169] AdViSHE[170] and TECH-VER.[171]

Overall, the results of this additional round of validation provides further confidence to the technical and conceptual validity of the model.

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B.3.12.2 *Validation with external clinical experts*

Clinical validation was sought for the analysis consisting of an ad-board held in January 2024, including 6 UK clinical experts. The clinical experts were practicing oncologists based in the UK and provided clinical input into the modelling assumptions and inputs. [22]

B.3.13 *Interpretation and conclusions of economic evidence*

A *de novo* economic model was developed to evaluate the cost-effectiveness of durvalumab with PDC as neoadjuvant treatment followed by durvalumab monotherapy as adjuvant treatment for patients with resectable NSCLC. This model comprehensively considers relevant costs, resources, and outcomes from a UK perspective. Its design is straightforward, mirroring the progression of the disease over time and aligning with structures utilised in other neoadjuvant, adjuvant and perioperative assessments in early-stage cancer reviewed by NICE.

The key strengths of this submission include:

- Incorporating the latest clinical data from the AEGEAN phase III RCT, demonstrating a statistically significant and clinically meaningful improvement in EFS.
- Utilising data from Checkmate-816 to assess the cost-effectiveness compared to standard of care (neoadjuvant nivolumab + PDC). Critically, the cost-effectiveness analysis of perioperative durvalumab versus neoadjuvant nivolumab + PDC utilises the outcomes from the MAIC, which accounts for key imbalances in the baseline characteristics between the AEGEAN and CheckMate-816 trial and provides a more robust estimate of the relative efficacy of these regimens.
- Presenting the cost-effectiveness outcomes of perioperative durvalumab versus neoadjuvant PDC, neoadjuvant nivolumab + PDC, surgery alone, and adjuvant PDC. All regimens were outlined in the final NICE scope.
- Conducting rigorous cost-effectiveness analyses, testing uncertainties through various scenarios to affirm conclusions about the cost-effectiveness of the technology (results were robust for all scenario analyses with only one extreme scenario [time horizon set at 15 years]).
- Incorporating data from prior NICE TAs whenever feasible to inform the efficacy in post-recurrence health states, ensuring alignment with evidence previously accepted by NICE and an accurate representation of the UK treatment pathway. For example, the DM health state utilises available data to inform the efficacy in a simplified modelling approach, whilst still captures the differences in pre-/post-progression within DM.
- Extensively validating model outcomes both internally and against external literature. This validation demonstrated the immaturity of the AEGEAN trial OS data.

One limitation in assessing this technology is the absence of long-term EFS and OS data beyond the trial's follow-up period, however this uncertainty has been addressed by exploring various methods to extrapolate EFS beyond the trial duration. EFS measures

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disease progression that prevents surgery, recurrence, or death, reflecting treatment success across neoadjuvant and adjuvant periods without being influenced by subsequent therapies. It aligns with treatment goals and can potentially serve as a surrogate for OS. Research demonstrates a strong association between EFS and OS, indicating their correlation and the impact of recurrence on OS neoadjuvant treatment.[172]

The improved EFS for patients treated with perioperative durvalumab resulted in an increase of [redacted] and [redacted] QALYs versus neoadjuvant PDC, neoadjuvant nivolumab + PDC, surgery alone and adjuvant PDC, accordingly in the probabilistic analysis. The prediction of improved long-term outcomes for perioperative durvalumab compared to neoadjuvant nivolumab + PDC demonstrates the value of the perioperative approach. The continuation of adjuvant IO post-surgery and neoadjuvant therapy, consolidates the immune response and sustains the suppression/eradication of micro metastases. Consequently, perioperative durvalumab presents a substantial increase in both life years and QALYs for a patient population with only neoadjuvant or adjuvant alone treatment options. The cost-effectiveness analysis indicates that perioperative durvalumab is cost-effective versus all comparators. The probabilistic ICER for perioperative durvalumab was £6,194, £23,625 and £4,872 per QALY versus neoadjuvant PDC, neoadjuvant nivolumab + PDC, and adjuvant PDC, respectively and dominant versus surgery alone. There is a [redacted] probability of cost-effectiveness of perioperative durvalumab versus neoadjuvant nivolumab + PDC at a WTP threshold of £30,000/QALY.

To conclude, the observed clinically meaningful improvement in EFS with perioperative durvalumab versus all other comparators provides extended life and increased opportunity for cure for patients at an early stage of the NSCLC treatment pathway, addressing a significant unmet medical need. Consequently, patients with resectable NSCLC could greatly benefit from the first NICE appraised perioperative treatment option, especially since there are currently no treatment options available that encompass both neoadjuvant and adjuvant immunotherapy treatment alone.

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B.4. References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

February 2024

File name	Version	Contains confidential information	Date
ID6220_Durvalumab_SIP_[noCON]_06FEB2024	2.0	No	14 February 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Durvalumab (IMFINZI®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The purpose of this submission to the National Institute for Health and Care Excellence (NICE) is to evaluate a new treatment regimen for people with non-small cell lung cancer (NSCLC). This new treatment regimen involves treating people's NSCLC with durvalumab in combination with chemotherapy before surgery to remove the cancer (called curative-intent surgery), then continuing treatment with durvalumab alone after surgery. Treatment is given in addition to surgery alone with the aim of further reducing the risk of cancer returning. Treatment before surgery is called neoadjuvant therapy and treatment after surgery is called adjuvant therapy. As this regimen involves treatment before and after surgery, it is called a perioperative treatment regimen. It is anticipated that perioperative durvalumab will be used to treat certain people with lung cancer that are: [1] • Adults diagnosed with NSCLC, specifically tumours that are at least 4 cm in size and/or the lymph nodes contain cancer cells (node positive) • The NSCLC is resectable, meaning the person is eligible to undergo surgery to remove the NSCLC in their lungs (this type of surgery is also known as resection) • Without known epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) gene mutations (these are explained in 2b Diagnosis of the condition)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The perioperative durvalumab regimen for the treatment of resectable NSCLC is under review by the Medicines and Healthcare Products Regulatory Agency (MHRA). Please refer to the Main Submission Document B, Section B.1.2 (Table 2) for the anticipated date of approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK Limited engages with the following patient advocacy groups in lung cancer, with the aims of strengthening patient insights and responding to requests for information: EGFR Positive UK and Roy Castle Lung Cancer Foundation. AstraZeneca UK is also a corporate supporter of UK Lung Cancer Coalition, which includes patient advocacy groups. Funding provided to UK patient groups is published annually on our website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Overview of NSCLC

Lung cancer is the third most common cancer and the most frequent cause of cancer deaths in the United Kingdom (UK).[2] The main types of lung cancer in the UK are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) but NSCLC is more common.[3]

The symptoms of lung cancer often don't appear straight away and when they do appear, it can be hard to recognise them as a symptom of lung cancer.[4,5] People with lung cancer commonly develop a new cough or a persistent cough, they may cough up blood or up phlegm (sputum) with blood in it, become short of breath easily, feel an ache or pain in the chest or shoulder, or experience chest infections that keep coming back or a chest infection that doesn't get better.[6]

Other symptoms of lung cancer that are less common can include losing appetite, feeling tired all the time (fatigue), losing weight, developing swollen fingers and nails (also known as finger clubbing and is more common in NSCLC), or experiencing pain and swelling in joints (this condition is called hypertrophic pulmonary osteoarthropathy [HPOA]).[6]

How many people have the condition

Section 1b describes the anticipated eligible population for perioperative durvalumab. For this population, it is estimated that 875 patients will be eligible and treated with perioperative durvalumab for resectable NSCLC based on:

- About 34,500 people are diagnosed with lung cancer in the UK each year[7]
- Of these new lung cancer cases, about 90% will be NSCLC and a further 15% to 20% will have surgery to remove the NSCLC[7]
- Approximately 30% of people with NSCLC are diagnosed with stage II-III disease (see 2b. Diagnosis of the condition below)[7,8]
- Between 8% to 16% of people with early-stage (stage III or less) NSCLC have EGFR mutations and will not be eligible for perioperative durvalumab. However, there is a targeted treatment option (osimertinib) that has significant survival benefits in this population[23-27]

Life expectancy

In England, only 2 out of every 10 people are alive 5 years after being diagnosed with lung cancer.[2] This is much lower than other common types of cancer such as breast and prostate in which closer to 9 out of every 10 people are alive 5 years after being diagnosed.[9,10]

Despite undergoing surgery to remove the cancerous tumour in the lung, for more than 60% of people with stage II or III disease, either the NSCLC will return or the person dies within 5 years of surgery.[11] In some people, the NSCLC can return quickly and the risk is the highest in the 12 months after surgery.[12,13] Once the NSCLC returns, the opportunities for further treatment with curative intent are limited and the chance of survival is generally poor:[13-15]

- The risk of death is 2.5 times higher for people whose NSCLC returns compared with people who stay cancer-free
- Less than 30% of people whose NSCLC comes back, live to 5 years

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is NSCLC diagnosed?

In the UK, NSCLC is diagnosed using a variety of tests. These might include all or some of the following: chest X-rays, bronchoscopy, computerised tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography CT (PET-CT), ultrasound scans, and lung cancer samples (biopsies).[16]

How is the severity of NSCLC determined?

At diagnosis, the severity of a person's NSCLC is determined by assessing the size of the tumour, whether lymph nodes are affected, and whether cancer has spread to other organs in the body. A stage is given that indicates disease severity that ranges from stage I (least severe, early-stage) to stage IV (most severe, advanced stage). People diagnosed with stage II or III NSCLC have cancer that is mostly localised in the lung but it may have spread to nearby lymph nodes.[17] Stage II or III cancers have not spread to other organs outside of the lungs.[17]

Testing for gene mutations in NSCLC

Some NSCLCs have changes in particular genes and proteins.[18] These changes (mutations) make the cancer grow and divide at a different pace than normal cells and cancer cells without such mutations, but these changes can also be used as targets for specific medicines. Changes in epidermal growth factor receptor (EGFR) (a protein on the surface of cells in the human body) and anaplastic lymphoma kinase (ALK) gene (a gene that provides instructions for making a protein called ALK on the surface of cells in the human body) are examples of changes in NSCLC and there are other effective treatments options available for people with these mutations.

Genetic testing for EGFR and ALK mutations is done on biopsies, small tissue samples from the cancer in the lung usually taken when the individual was first diagnosed or from tissue removed during surgery. People are routinely tested for EGFR and ALK in the UK.[16,19]

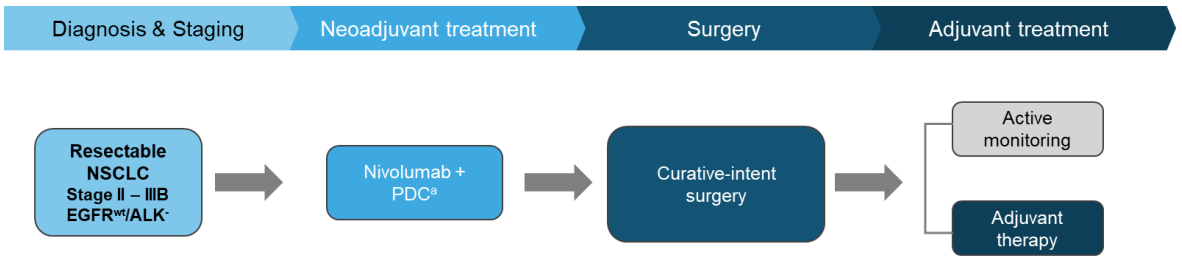
2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The current treatment pathway for people with resectable NSCLC and no known change in the EGFR or ALK is shown in **Figure 1**. This treatment pathway is based on the NICE guideline for the management and treatment of NSCLC, last updated in March 2023, and relevant technology appraisal guidance for treatments used before and after surgery.[16,20,21]

Figure 1. Current treatment pathway for resectable NSCLC



Abbreviations: ALK-, absence of change in the anaplastic lymphoma kinase gene; EGFRwt, absence of change in the epidermal growth factor receptor protein (wild-type protein); NSCLC, non-small cell lung cancer; PDC, platinum-doublet chemotherapy

[a] Stage IB-IIIA, resectable (tumours ≥4 cm or node positive) NSCLC

The main treatment for people with NSCLC is surgery to completely remove the tumour for those who are fit enough to undergo such treatment.[16] People may have surgery alone or they may receive additional treatments either before or after surgery with the aim of reducing the chance of the NSCLC returning and increasing the chance of living longer.[14,22] These current options include either: 1) neoadjuvant nivolumab plus chemotherapy, 2) neoadjuvant chemoradiotherapy (chemotherapy in combination with radiotherapy) for a small proportion of people, or 3) adjuvant chemotherapy.[16] These current treatment options have limitations that are described below. All people are actively monitored after surgery regardless of whether they receive adjuvant therapy or not.[16]

- **The recommendation for nivolumab is for use before surgery only**

Nivolumab plus chemotherapy was recommended by NICE in March 2023 as a neoadjuvant treatment for people with stage IB-IIIA resectable (tumours ≥4 cm or node positive) NSCLC.[20] Nivolumab is a treatment that is from the same family of medicines as durvalumab, they are immuno-oncology therapies (see Section 3a). The recommendation for nivolumab for use before surgery only does not address the need for treatment after surgery that continues to prevent the growth and spread of micrometastases at the time the risk of NSCLC returning is the highest.

- **Chemoradiotherapy before surgery is only recommended for a small number of people with specific disease characteristics**

The only neoadjuvant chemotherapy recommended in the UK is chemoradiotherapy for people with specific disease characteristics (resectable, stage IIIA-N2 NSCLC only meaning the tumour has not spread to other organs but it has spread to lymph nodes that may be difficult to remove with surgery as they are located near the lungs and heart).[16,23] For that reason, chemoradiotherapy in either a neoadjuvant or adjuvant setting is only used in around 5% of stage IIIA NSCLC in England.[24] A group of UK clinicians have confirmed that neoadjuvant chemoradiotherapy is not offered to patients with resectable NSCLC in UK clinical practice.[25]

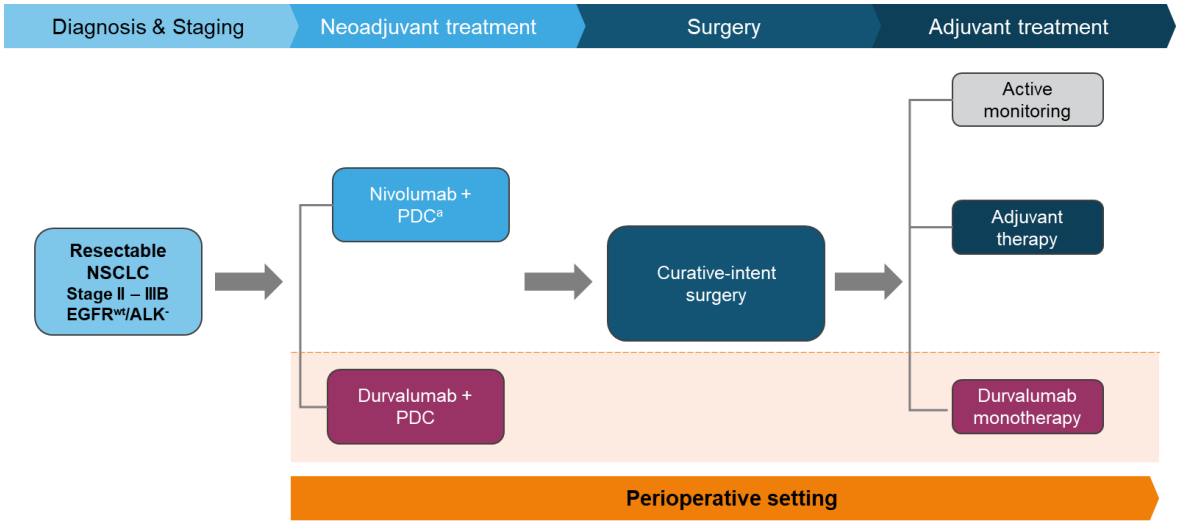
- **Chemotherapy after surgery offers only small improvements in survival and it is only suitable for some patients**

In the UK, adjuvant platinum-based chemotherapy (medications used to treat cancer that contain the element platinum) is recommended for people with a good performance status (World Health Organisation [WHO] 0 or 1), a tumour size between 4cm and 5cm, and when the tumour has not spread to lymph nodes or outside lungs).[16,23] However, chemotherapy is associated with several side effects and a large proportion of eligible people either choose not to have chemotherapy or are not fit enough to tolerate it following surgery.[26] Around 13%, 44%, and 50% of people in stage IB, II, and IIIA NSCLC, respectively, receive adjuvant chemotherapy in the UK.[27] In comparison with people who receive surgery alone, the addition of chemotherapy after surgery offers only minimal

benefits in terms of prolonging the life of people with NSCLC. At 5 years after surgery, 64% of people were alive that received adjuvant chemotherapy after surgery and 60% of people were alive who underwent surgery only i.e., a difference of 4%.[22]

As a result of these limitations, current treatments may not be enough to reduce the risk of NSCLC returning after resection. **Figure 2** shows the current treatment pathway with the addition of perioperative durvalumab. The benefits of a perioperative immuno-oncology regimen are described in Section 3a below. As demonstrated by the results of AEGEAN (see Section 3e) and compared to other therapies in the treatment pathway (by indirect comparison [see Section 3e]), perioperative durvalumab may reduce the risk of NSCLC returning or death,[28] and therefore improve the possibility of successful long-term outcomes, including cure. In addition, the side effects experienced by the people taking durvalumab are usually mild and they are consistent with what is expected for this medicine.[28] As such, perioperative durvalumab as an additional treatment option in the current pathway of care can address the substantial unmet need among people who, despite undergoing surgical removal of the tumour, have NSCLC that returns.[11]

Figure 2. Proposed place of perioperative durvalumab in the treatment pathway for resectable NSCLC



Abbreviations: ALK-, Absence of change in the anaplastic lymphoma kinase gene; EGFRwt, Absence of change in the epidermal growth factor receptor protein (wild-type protein); NSCLC, non-small cell lung cancer; PDC, platinum-doublet chemotherapy

[a] Stage IB-IIIA, resectable (tumours ≥4 cm or node positive) NSCLC

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The quality of life of people with NSCLC can be affected in various ways. Some people may experience persistent symptoms after curative surgery, such as shortness of breath (dyspnoea)

and tiredness (fatigue), or develop physical limitations that mean they have to stop or reduce their normal daily activities.[29-31] People with NSCLC who are of working age may be required to take a long-term absence from work, disability leave, or permanent disability.[32] Having to adapt to new roles within the family, socially, or professionally, or changes to routines as a result of physical limitations can also affect people's mental health.[31]

People who have lung cancer commonly have other medical conditions (comorbidities) in addition to their lung cancer that are also burdensome.[33] Examples of these comorbidities include heart disease, respiratory-related diseases (e.g., chronic obstructive pulmonary disease or asthma), anxiety, and depression.[33-36]

Most people (>80%) live with the fear of their cancer coming back after surgery which can cause anxiety and distress.[31,37] If a person's NSCLC does return despite curative surgery, their quality of life decreases further.[11,30,38] When NSCLC returns and spreads to other organs of the body, in particular the brain and bone, it can be very painful and cause other severe symptoms, further reducing normal daily functioning, and substantially reducing the chance of survival.[39,40]

Caregivers of people with NSCLC experience a considerable burden associated with care that can worsen over time.[41,42] As a result of the long-term consequences of NSCLC (for example persistent shortness of breath or reduced physical ability), caregivers of people with NSCLC also need to adapt to new roles and responsibilities within family life that can be emotionally burdensome.[31]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The Summary of Product Characteristics for durvalumab is available here: https://www.medicines.org.uk/emc/product/9495/smpc#gref

Durvalumab is an immuno-oncology therapy that is designed to recognise a specific target protein in the body to help people's immune system fight their cancer.[43]

There is a protein found on the surface of T cells (a type of immune cell), called programmed cell death-1 (PD-1). The PD-1 protein interacts with another protein found on cancer cells or immune cells called programmed cell death ligand-1 (PD-L1). This PD-1 and PD-L1 interaction reduces T cell activity and prevents the body's immune system from attacking the cancer cells. Durvalumab is a drug that binds to the PD-L1 protein and blocks the interaction with PD-1, thereby increasing the activity of T cells and the immune system's ability to attach to and destroy cancer cells.

There is evidence from clinical studies that shows immuno-oncology therapies can prolong the time people with resectable NSCLC stay alive and cancer free when used either before surgery or after surgery.[44-46] A perioperative regimen, treating with the same immuno-oncology therapy (durvalumab) before and after surgery, may further these benefits as it can: [12,13,47-49]

- Prepare a person's immune system before surgery, which means the body's immune system is ready to recognise and destroy cancer cells more quickly at a later time (after surgery)

- Prevents the growth and spread of micrometastases (cancer cells that have spread but are too small to see on scans)[50] before, and after surgery when the risk of NSCLC returning is the highest

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

The neoadjuvant (before surgery) part of the perioperative treatment regimen with durvalumab will be in combination with chemotherapy.[1] Standard chemotherapies used in the treatment of NSCLC before surgery include platinum-based chemotherapy medicines, commonly cisplatin and carboplatin.[16]

Several preclinical studies (research for treatment for a disease that occurs before it is tested on human volunteers) show that immuno-oncology therapies can stimulate and strengthen the immune system and the response of the immune system to tumours, when they are given before surgery.[47] Conventional chemotherapy medicines directly kill tumour cells or stop them from dividing. However, under specific conditions, chemotherapy medicines may heighten the immune-stimulation effect of immuno-oncology therapies and improve the immune response to tumour cells. Combining these two medicine groups may mean more tumour cells are killed when given at tolerated doses.[51]

The side effects associated with platinum-based chemotherapy agents include increased risk of getting an infection, breathlessness, looking pale, bruising, bleeding gums, nose bleeds, feeling or being sick, changes to liver and kidney, and abdominal pain and cramps[52,53]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Durvalumab is a medicine that is given through an infusion (drip) that goes into a vein in people's arm or to a large vein in the chest.[1,54]

Durvalumab is recommended to be given in combination with platinum-based chemotherapy over 1 hour at a dose of 1,500 mg every 3 weeks for up to 4 cycles prior to surgery, followed by 1,500 mg as monotherapy (alone) every 4 weeks for up to 12 cycles after surgery.[1]

The medicine is given until the tumour becomes unresectable, until the tumour returns, or until the doctor stops treatment due to intolerable side effects, or for a maximum of 12 cycles after surgery.[1] When given in combination with chemotherapy durvalumab is given first followed by chemotherapy.[54]

People with resectable NSCLC with a body weight of 30 kg or less must receive durvalumab at a weight-based dosing of 20 mg/kg. When given in combination with platinum-based chemotherapy, the dose of durvalumab is recommended at 20 mg/kg body weight every 3 weeks (21 days) prior to surgery, followed by monotherapy at 20 mg/kg every 4 weeks after surgery until the weight of the person receiving the medicine increases to greater than 30 kg.[1]

Receiving durvalumab directly into the veins can cause side effects associated with infusion presenting as chills or shaking, dizziness, itching or rash, feel like passing out, flushing, fever, shortness of breath or wheezing, and/or back or neck pain.[55] These can be managed by stopping the medicine infusion or slowing down the rate of medicine infusion. Doctors may also provide medicines such as corticosteroid before durvalumab infusion to prevent such side effects in future treatment cycles.[1] The other treatments that can be given before or after surgery are also administered directly into the veins and patients may experience side effects associated with these infusions as well.[52,56]

Infusions of cancer medicines that are given directly into the veins are usually done at a cancer day clinic or hospital and can take a few hours. A friend or family member can accompany the person receiving treatment.[57]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

AEGEAN, the study is currently ongoing [58]

Table 1. Study - AEGEAN (NCT03800134)

Study	AEGEAN[28,58]
Title:	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)
Status	Active, not recruiting
Study design	AEGEAN is an ongoing, phase 3, double-blind, placebo-controlled, randomised, multi-center, international study
Settings and locations	231 sites in 28 countries (Argentina, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Costa Rica, France, Germany, Hungary, India, Italy, Japan, Mexico, Netherlands, Peru, Philippines, Poland, Republic of Korea, Romania, Russian Federation, Spain, Taiwan, Thailand, the United States of America [US], Vietnam)
Population	<u>Key inclusion criteria</u> • Adults of age ≥18 years with resectable NSCLC (Stage IIA to select (N2) Stage IIIB) expressing PD-L1 protein on surface of tumour cells and have a WHO/ Eastern Cooperative Group Performance status (ECOG PS) of 0 or 1 at enrolment • Had not received any previous treatment for the tumour <u>Key exclusion criteria</u> • People who have Stage IIIB N3 and Stages IIIC, IVA, and IVB NSCLC

	• People with unresectable NSCLC or change in the EGFR or ALK protein • People with more than one primary tumour such as mixed small-cell and NSCLC • People who have primary immunodeficiency disease, autoimmune or inflammatory disorders, HIV or hepatitis B or C infections • People who have received allogenic organ transplantation or radiotherapy before surgery • People whose tumour has spread to brain or spinal cord • People with allergy or hypersensitivity to durvalumab or any of its components	
Number of people in the study	There were 740 people randomly assigned to the study treatments, 366 people in the perioperative durvalumab group and 374 in the perioperative placebo group	
Intervention	Durvalumab plus platinum-based doublet* chemotherapy prior to surgery then durvalumab alone after surgery * Platinum-doublet chemotherapy is the combination of a platinum containing agent with another type of chemotherapy such as a taxane or gemcitabine. In AEGEAN, the combinations were: carboplatin/paclitaxel, cisplatin/gemcitabine, pemetrexed/cisplatin, or pemetrexed/carboplatin	
Comparator	Placebo plus platinum-based doublet chemotherapy* then placebo alone after surgery *In AEGEAN, the combinations of platinum doublet chemotherapy were: carboplatin/paclitaxel, cisplatin/gemcitabine, pemetrexed/cisplatin, or pemetrexed/carboplatin) prior to surgery	
Estimated study completion date	September 11, 2028	
References for further information	Please refer to the following source for further details: U.S. National Library of Medicine. A Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients with Resectable Non-small Cell Lung Cancer (AEGEAN). ClinicalTrials.gov Identifier: NCT03800134. https://classic.clinicaltrials.gov/ct2/show/NCT03800134	

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition. In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.
The evidence for the efficacy of perioperative durvalumab for the treatment of resectable NSCLC comes from one clinical trial and indirect treatment comparisons.

Evidence from clinical trials

The efficacy and safety of perioperative durvalumab have been studied in the clinical trial AEGEAN. In AEGEAN, participants had resectable NSCLC stage IIA-IIIB[N2], which means they had tumours that can be removed by surgery. Participants took durvalumab plus platinum-based doublet chemotherapy before surgery, followed by surgery to remove the tumour, and then durvalumab monotherapy after surgery, or placebo (a dummy drug with no active ingredient) plus platinum-based doublet neoadjuvant chemotherapy followed by placebo alone after surgery after having their tumours removed by surgery.[28]

Hereafter, for simplicity, perioperative (received before and after surgery) durvalumab plus neoadjuvant chemotherapy and placebo plus neoadjuvant chemotherapy will be referred to as the perioperative durvalumab and perioperative placebo arms, respectively.

The results for AEGEAN are presented for the group of study participants that did not have EGFR or ALK mutations. This group was called the modified intent-to-treat (mITT) population as it excluded participants who were initially included in the overall study population.[28] The mITT population included 740 adults who were randomly assigned to the perioperative durvalumab or perioperative placebo arms; 366 were treated with perioperative durvalumab and 374 were given perioperative placebo. Neither the participant nor their doctor knew which treatment they were taking. The treatment durvalumab/placebo plus chemotherapy was given every 3 weeks for 4 cycles before surgery and durvalumab monotherapy/placebo alone was given every 4 weeks for up to 12 cycles after surgery.[28]

The primary aims of AEGEAN were to see how long participants in the study with resectable NSCLC stage IIA-IIIB[N2] would remain alive and cancer-free with perioperative durvalumab treatment (known as event-free survival [EFS]) and how many participants in the study will not have any viable tumour cells (known as pathological complete response [pCR]), after having their tumours completely removed by surgery.[28,59-61]

Primary outcome: event-free survival (Document B: B.2.6.1)

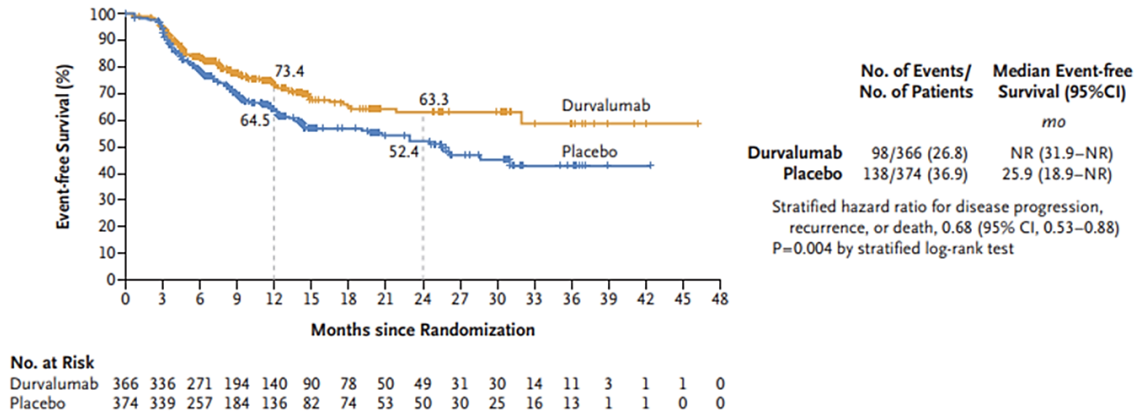
EFS is an important clinical trial endpoint in resectable NSCLC as it measures if a treatment is successful in preventing the return of NSCLC. In AEGEAN, EFS is defined as the time from when the participant is randomised to receive a study treatment until evidence of disease recurrence, discontinuation of the study treatment for any reason, or death.[28] EFS is measured over the period of the clinical trial and is a good indication that the treatment may help people survive in the long term.[62-66] It was therefore chosen as the primary aim of AEGEAN.

AEGEAN showed that participants in the perioperative durvalumab arm stayed cancer-free and alive for longer compared with those participants in the perioperative placebo arm:[28]

- At the first interim analysis of EFS (data cut-off [DCO] 10 November 2022), median EFS in the perioperative durvalumab arm was not reached and was 25.9 months in the perioperative placebo arm (hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.53 to 0.88; p=0.004)
- This means that participants taking perioperative durvalumab were 32% less likely to have their cancer come back or die compared with those taking perioperative placebo

A Kaplan-Meier (KM) plot shows the rate at which an event, in this case, the return of NSCLC or death, occurs over time. A steeper downward slope indicates a higher event rate and therefore a worse prognosis. The KM plot in **Figure 3** below shows the curves for perioperative durvalumab and perioperative placebo overlap until 3 months, then shows a clear and sustained separation, showing that a greater number of participants taking perioperative durvalumab remained alive and cancer-free for a longer time compared with those who were given perioperative placebo.[28]

Figure 3. KM plot of EFS, mITT population



DCO 10 November 2022 (N=740)

Abbreviations: CI, confidence interval; DCO, data cut-off; EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat; NSCLC, non-small cell lung cancer; NR, not reached

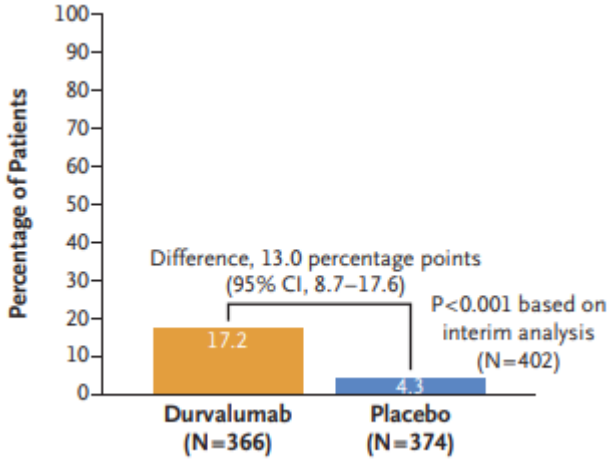
Source: Heymach et al. 2023[28]

Primary outcome: pathological complete response (Document B: B.2.6.2)

The second primary aim of AEGEAN, pCR, is an early and stringent indication of how well the tumour is responding to the medicine when used in the period before surgery and is closely related to how long people live.[60,62-64] It was therefore chosen as the primary aim of AEGEAN.

AEGEAN showed that a higher number of participants in the perioperative durvalumab arm did not have viable tumour cells than participants in the perioperative placebo arm (17.9% versus 4.9%, respectively).[28] This difference was 13.0% as shown in Figure 4 below.

Figure 4. pCR at final analysis, mITT population



DCO 10 November 2022 (N=740)

Abbreviations: CI, confidence interval; DCO, data cut-off; mITT, modified intention to treat; pCR, pathological complete response

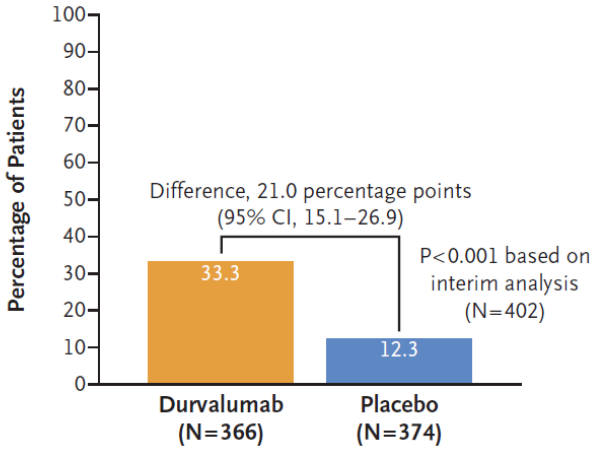
Source: Heymach et al. 2023 [28]

Secondary outcome: major pathological response (Document B: B.2.6.3)

Similar to pCR, major pathological response (MPR) is also related to how long people live and remain disease-free.[60] It indicates that people have 10% or fewer remaining viable tumour cells in the surgically removed tumour-affected lung and lymph node tissue.[60]

The AEGEAN study showed that a higher number of participants in the perioperative durvalumab arm had ≤10% remaining viable tumour cells after surgery than participants in the perioperative placebo arm (34.2% versus 14.1%, respectively). This difference was 20.1% as shown in Figure 5 below.[28]

Figure 5. Major pathological response at final analysis, mITT population



DCO 10 November 2022 (N=740)

Abbreviations: CI, confidence interval; DCO, data cut-off; mITT, modified intention to treat

Source: Heymach et al. 2023 [28]

Surgical outcomes (Document B: B.2.6.5)

It is important that treatments taken prior to surgery do not lead to delays to surgery (as this may result in the disease growing or spreading to an extent in which surgery can no longer be performed) or increase the risk of surgical complications.[67] The AEGEAN study showed that: [28]

- Most participants were able to undergo R0 resection, meaning that after surgical removal of the tumour there was no evidence microscopic disease that remained (94.7% in the perioperative durvalumab arm and 91.3% in perioperative placebo)
- A slightly higher number of participants in the perioperative durvalumab arm underwent surgery without any delays than those in the perioperative placebo arm (82.7% and 77.8%, respectively); however, the median time from the last neoadjuvant medicine dose to surgery was the same for participants who were given perioperative durvalumab or perioperative placebo (34.0 days)
- Of the participants that did experience a delay to surgery (perioperative durvalumab, 17.3% and perioperative placebo, 22.2%), most delays were less than 2 weeks in both treatment arms

Information to note while interpreting efficacy results

- AEGEAN started in 2018 and is estimated to end in 2028.[58] The results of AEGEAN presented here are from early planned analyses. AEGEAN is ongoing and will provide further evidence for longer-term EFS, as well as disease-free survival (another study endpoint that measures how long people with cancer remain tumour-free) and overall survival (OS) at future planned analyses. The first interim analysis of EFS was conducted when 31.9% of participants in the study experienced tumour recurrence or death.[28] At this point, the participants in the study had been monitored over a median time of 11.7 months.[28]
- AEGEAN aimed to evaluate perioperative durvalumab in a population that closely resembled people who will receive the treatment in real-world clinical practice. AEGEAN includes more than 700 participants from multiple countries with approximately 40% of

participants enrolled in Europe, 40% in Asia, 10% in North America, and 10% in South America.[28] On average, participants in AEGEAN are slightly younger than people with lung cancer in the UK (median age was 65 years in AEGEAN and 74 years in UK clinical practice).[7,28] To be eligible for inclusion in AEGEAN, participants had to have a good performance status (Eastern Cooperative Group Performance status (ECOG PS) of 0 or 1) i.e., their NSCLC does not affect their ability to perform daily activities.[28] In UK clinical practice, people with lung cancer have ECOG PS scores that range from 0 to 4 (with 4 representing people whose lung cancer severely inhibits their ability to perform daily activities).[7] These differences in age and performance status between clinical trial and real-world populations are observed in most clinical trials for cancer treatments and are not expected to impact the interpretation of the efficacy and safety results of AEGEAN. UK clinical experts agree that the AEGEAN study population is entirely generalisable to patients seen in UK clinical practice.[25]

Evidence from indirect treatment comparisons

AEGEAN does not directly compare perioperative durvalumab with all the therapies currently in the treatment pathway in the UK. In AEGEAN, perioperative durvalumab is compared against a perioperative placebo control arm with both study arms receiving chemotherapy in the neoadjuvant phase.[28] In UK clinical practice, other treatment options include neoadjuvant nivolumab plus chemotherapy, adjuvant chemotherapy, or surgery alone.[16]

Indirect treatment comparisons are a way of comparing treatments that have not been directly compared against each other in a clinical trial and when a common comparator has been used in the respective studies. For example, treatment A is compared with treatment C in Study 1 and treatment B is compared with treatment C in Study 2. Using a common comparator of treatment C and the information from Studies 1 and 2, how well treatment A compares against treatment B can be estimated.

Indirect comparison versus treatment options available in UK practice (Document B: B.2.9)

The indirect comparison of perioperative durvalumab compared with neoadjuvant nivolumab plus chemotherapy, or adjuvant chemotherapy plus surgery, demonstrated that perioperative durvalumab can lower the risk of NSCLC returning or death. Details about the methods and results are confidential and presented in Document B, section B.2.9.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In the AEGEAN trial, participants' quality of life was measured using generic and lung cancer-specific questionnaires. These included the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EORTC QLQ- Lung Cancer 13 (LC13), and the EuroQol 5-dimension questionnaire (EQ-5D). The rationale for using a generic questionnaire was that people in AEGEAN, who have no evidence of disease after surgery, predominantly don't have

any symptoms and the different aspects of physical and mental health of these people are better captured with a generic quality of life questionnaire.[68]

The impact that perioperative durvalumab has on participant HRQoL in AEGEAN is reported in Document B, B.2.6.4.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like any medicine, durvalumab can cause side effects, although not everybody gets them. How often and how severe the side effects are can vary from person to person. In AEGEAN, perioperative durvalumab was generally well tolerated.[69] The use of perioperative durvalumab with neoadjuvant chemotherapy did not affect people's ability to undergo four cycles of any chemotherapy.[28] The addition of durvalumab to chemotherapy also did not affect the occurrence or severity of side-effects possibly related to surgery, or with any complications of the surgery.[70]

More than 80% of people, i.e., 87.3% of people who received perioperative durvalumab and 89.7% who received perioperative placebo in AEGEAN completed their treatment regimens (i.e., got all planned rounds of durvalumab/placebo and chemotherapy).[28] The safety of perioperative durvalumab plus neoadjuvant chemotherapy was examined among 799 people,[69] and the side-effects following surgery was assessed among 597 people.[70]

Most participants in both the perioperative durvalumab and perioperative placebo arms experienced a side effect in AEGEAN (96.5% and 94.7%, respectively). However, more than 50% of participants in both study arms experienced side effects that were mild or moderate in severity.[28] Anaemia, nausea, and constipation were the most commonly experienced side-effects by participants (≥20%) in the perioperative durvalumab arm in AEGEAN (Table 2).[28] Side-effects affecting the immune system were experienced by 95 participants (23.7% of 401) who received perioperative durvalumab and 37 participants (9.3% of 398) who received perioperative placebo.[28]

Table 2. Most common AEs (≥20% of people in either treatment group) in AEGEAN

Side effect	Symptoms	Perioperative durvalumab (n=401)	Perioperative placebo (n=398)
Anaemia	Breathlessness and looking pale due to a low number of red blood cells	136 (33.9%)	126 (31.7%)
Nausea	Feeling an urge to vomit	101 (25.2%)	115 (28.9%)
Constipation	Difficulty in passing stools	100 (24.9%)	84 (21.1%)

DCO 10 November 2022 (n=799)

Source: Heymach et al. 2023[28]

A total of 48 participants (12.0% of the 401 in the perioperative durvalumab arm) discontinued the treatment with durvalumab and chemotherapy due to side effects.[28] Only 7 participants (1.7% of the 401 in the perioperative durvalumab arm) experienced side effects that caused cancellation of surgery.[28] Further, 23 participants (5.7% of the 401 in the perioperative durvalumab arm) died due to side effects, but these side effects were not considered related to treatment with durvalumab.[28]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

The key benefits of perioperative durvalumab for people with resectable NSCLC, their families, and caregivers include:

- Primes a person's immune system before surgery, which means the body's immune system is ready to recognise and destroy cancer cells more quickly at a later time (after surgery)
- Prevents the growth and spread of micrometastases before, and after surgery when the risk of NSCLC returning is the highest
- Compared with other therapies in the current treatment pathway, perioperative durvalumab potentially lowers the risk of NSCLC returning or death and therefore improves the possibility of successful long-term outcomes, including cure
- Treatment with perioperative durvalumab does not delay or change the type of planned surgery to remove the NSCLC; most people will still undergo R0 resection, surgery that removes the tumour and leaves no evidence of microscopic disease
- As seen in AEGEAN, the side effects of perioperative durvalumab are expected to be manageable, mostly mild or moderate in severity, consistent with side effects that have been seen for this treatment when used to treat other types of cancer, and are unlikely to result in the person having to stop their treatment
- Although this is not studied in the AEGEAN trial, it is anticipated that the quality of life of the families and caregivers of people who are treated with perioperative durvalumab is likely to be maintained as their loved ones stay tumour-free for longer, thereby avoiding the physical and emotional burden of caring for someone whose cancer has come back and spread

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

- The data on how long people live after treatment with perioperative durvalumab are not yet available
- In general, the treatment of resectable NSCLC with perioperative durvalumab does not have known disadvantages compared with existing therapies

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic model used four health states to represent the different phases of NSCLC. All patients start from the event-free (EF) health state before receiving surgery and remain in this health state unless the cancer returns or the patient dies. If the cancer returns, this can be either locally (where the cancer comes back in the same place it first started) or as distant metastasis (whereby the cancer returns in another part of the body). These two types of metastasis are represented in the model via the locoregional recurrence (LRR) and distant metastasis (DM) health states, accordingly. Death is considered the final health state, accounting for modelled patients who die either from NSCLC or from natural causes.

Perioperative durvalumab is given as neoadjuvant therapy before surgical resection of the tumour and also as adjuvant therapy after surgery. Surgery in early NSCLC is expected to make patients cancer-free, and the objective of treatment with durvalumab is to prolong this cancer-free period and subsequently extend life.

The economic model uses data from the AEGEAN study of perioperative durvalumab vs. placebo to estimate the probability of patients leaving the EF health state. When the cancer returns locally, patients enter the LRR health state and the probability of leaving this health state is informed by data coming from a combination of sources including published literature (PROCLAIM, US National Cancer Data Base studies and a meta-analysis)[15,71,72] and PACIFIC trial (pivotal trial for durvalumab in locally advanced NSCLC).[73] For the DM health state, published data from the pivotal trials of standard of care in metastatic NSCLC, i.e., pembrolizumab monotherapy

or in combination with chemotherapy, were used.[74-76] If patients remain in the EF health state for 5 years or longer, the model considers them to be functionally cured.[25]

To model how patients move through different health states, survival data from the above studies were used. Given that the available data from the studies cover the survival in the first few years, the model uses mathematical functions to predict how the disease course develops in the long-term. This approach adheres to standard practices and guidance from the NICE decision support unit (DSU).[77]

Alongside clinical outcomes, as described above, the model also captures changes in quality of life related to treatment with perioperative durvalumab. The EQ-5D-5L questionnaire was used in the AEGEAN trial to estimate patients' quality of life.[78] This is an instrument that comprises of five dimensions including mobility, self-care, usual activities, pain/discomfort and anxiety/depression with five level of responses, from no problems to extreme problems. In the model, quality of life is different across the different disease stages; it is higher in the EF and LRR health states and lower in the DM health states. Since patients receiving treatment with perioperative durvalumab remain event-free longer,[28] they also have improved quality of life.

The model accounts for costs related to treatments and use of healthcare services. Patients remain alive on treatment with perioperative durvalumab longer than other treatments in NSCLC due to its beneficial effect, however this also means that treatment-related costs are higher. For costs related to healthcare services, the model assumes that these are independent of the treatment being received. Patients in general use health services more frequently at more advanced stages of the disease, therefore the model estimates a greater cost in these states.

The model uses data from the AEGEAN, PACIFIC studies and published data from other studies,[15,68,71-76] which only have data available for the first few years of the disease. To estimate the lifetime impact over the course of the disease, different mathematical functions were used and tested as scenarios. These scenarios indicated that the impact on the results (calculated as incremental cost-effectiveness ratios or ICERs) was small.

The model shows that perioperative durvalumab improves event-free survival and quality adjusted life years compared to neoadjuvant chemotherapy. Perioperative durvalumab is more expensive than the other treatments before and after surgery in NSCLC, and combined with the increased quality of life, an incremental cost effectiveness ratio can be calculated.

Perioperative durvalumab costs £4,708, £19,575, and £4,458 per QALY compared to neoadjuvant chemotherapy, neoadjuvant nivolumab plus chemotherapy, and adjuvant chemotherapy, accordingly. Perioperative durvalumab is dominant (i.e., less costly, and more effective) in costs and quality adjusted life years gained compared to surgery alone (i.e., active monitoring). It should be noted that the ICERs that the committee consider may be different to the ICERs shown in the SIP due to comparator discounts or differences in preferred modelling assumptions.

Based on the evidence available and the company's economic analysis, perioperative durvalumab for patients with early-stage resectable NSCLC without known EGFR or ALK gene mutations, will be examined by NICE in this appraisal. The committee's decision will be based on the available data for perioperative durvalumab in this setting.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
The current treatment pathway for people with resectable NSCLC in the UK does not include a perioperative treatment regimen.[16] It is anticipated that durvalumab will be the first immuno-oncology therapy to be used for the perioperative treatment of resectable NSCLC and as such, is considered a step change in the treatment pathway in the UK. There are not many NICE-recommended treatment options for people with resectable NSCLC.[16] Until recently, there was no NICE-recommended neoadjuvant treatment (before surgery) for most people with resectable NSCLC, only chemotherapy combined with radiotherapy for a limited number of people with stage IIIA N2 disease.[16] Neoadjuvant nivolumab plus chemotherapy is now recommended by NICE (2023).[20] There has been little change in recommended treatments after surgery with adjuvant chemotherapy for eligible people or active monitoring remaining the current standard of care.[16] Despite being the standard of care, chemotherapy treatments that are used after surgery only have a small survival benefit over surgery alone.[14,22] Perioperative durvalumab has the ability to prime a person's immune system before surgery and prevent the growth and spread of micrometastases before, and after surgery when the risk of NSCLC returning is the highest (see Section 3a).[47-49] The evidence presented in this submission to NICE demonstrates perioperative durvalumab lowers the risk of NSCLC returning or death and therefore improves the possibility of successful long-term outcomes, including cure.[28] As such, it is considered innovative over current treatments for resectable NSCLC that are used only before or after surgery.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality issues are anticipated.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE

assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adjuvant: Treatment offered after surgery.

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.

ALK gene: Anaplastic lymphoma kinase gene, a gene that provides instructions for making a protein called ALK on the surface of cells in the human body.

Biopsy: A process in which a very small part of tissue in the body is removed to look for signs of disease.

Clinical trial/clinical study: A type of research study that tests how well new medical treatments work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study. When it is called "phase III clinical trial" it tests the safety and how well a new treatment works compared with a standard treatment. For example which group of people have better survival rates or fewer side effects. In most cases, treatments move into phase III clinical trials only after they meet the goals of phase I and phase II clinical trials. Phase 3 clinical trials may include hundreds of people.

CNS: Central nervous system.

CT scan / computerized axial tomography scan: A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly. A computerized axial tomography scan may be used to help diagnose disease, plan treatment, or

find out how well treatment is working. Also called CAT scan, computed tomography scan, computerized tomography, and CT scan.

Curative intent: a treatment given to a person that aims to destroy or get rid of all cancer cells in the body.

DFS: Disease-free survival, how long people with cancer would remain tumour-free. In a clinical trial, this is defined as the time from when the participant is randomised to receive a study treatment until evidence of disease recurrence

ECOG PS: Eastern Cooperative Group Performance status, standard criteria for measuring how a disease impacts a person's daily living abilities

EFS: Event-free survival, how long people with cancer would remain alive and tumour-free. In a clinical trial, EFS is defined as the time from when the participant is randomised to receive a study treatment until evidence of disease recurrence, discontinuation of the study treatment for any reason, or death.

EGFR: Epidermal growth factor receptor, a protein on the surface of cells in the human body.

EORTC QLQ- LC-13: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13.

EMA: European Medicines Agency: The regulatory body that evaluates, approves, and supervises medicines throughout the European Union.

EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – Cance Module.

EQ-5D: EuroQol 5-dimension questionnaire.

Follow-up duration: The stated length of time a person's health was monitored over time after treatment.

Health-related quality of life: The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living.

HTA: Health Technology Assessment (bodies): Bodies that make recommendations regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

Immuno-oncology therapy/Immunotherapy: A type of cancer therapy using substances made by the body or in a laboratory to boost the immune system and help the body find and destroy cancer cells.

Lymph nodes: the lymph nodes are small glands that are part of the body's lymphatic system that carry immune cells that help fight infections or cancer cells. Cancer cells can either start in lymph nodes or spread to the nodes from elsewhere in the body, e.g., the lungs.

MPR: Major pathological response, presence of ≤10% remaining viable tumour cells in the surgically removed tumour-affected lung and lymph node tissue.

Micrometastases: Cancer cells that have spread but are too small to see on scans.

MHRA: Medicines and Healthcare Products Regulatory Agency: The regulatory body that evaluates and approves medicines in the UK.

MRI: A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. MRI makes better images of organs and soft tissue than other

scanning techniques, such as computed tomography (CT) or x-ray. MRI is especially useful for imaging the brain, the spine, the soft tissue of joints, and the inside of bones. Also called magnetic resonance imaging, NMRI, and nuclear magnetic resonance imaging.

Neoadjuvant: Treatment offered before surgery.

NSCLC: Non-small cell lung cancer.

OS: Overall survival, how long people with a disease live.

pCR: Pathological complete response, absence of any viable tumour cells.

Performance status: A score that estimates the people's ability to perform certain activities of daily living without the help of others.

PET-CT: Positron emission tomography computed tomography.

Placebo: A dummy drug with no active ingredient.

Platinum-based chemotherapy: Medications used to treat cancer that contain the element platinum. This includes medicines like carboplatin, cisplatin etc.

Platinum-based doublet chemotherapy: Medication regimen used to treat cancer that contains a combination of platinum-containing agents with a taxane or gemcitabine or others.

Resectable: Tumour that can be removed by surgery.

Stage: A description of how severe a disease is.

Targeted therapy: A type of cancer treatment that targets specific proteins that control how cancer cells grow, divide, and spread. These treatments are designed to fix specific unhealthy areas in the body, such as cells with a specific mutation, for example, an EGFR mutation, while limiting damage to healthy parts of the body.

Treatment cycle: A cycle is the time between one round of treatment until the start of the next.

Unresectable: Tumour that cannot be removed by surgery.

X-ray imaging: A procedure that uses a type of high-energy radiation called x-rays to take pictures of areas inside the body. X-rays pass through the body onto film or a computer, where the pictures are made. The tissues and organs usually appear in various shades of black and white because different tissues allow different amounts of the x-ray beams to pass through them. X-ray imaging is used to help diagnose disease and plan treatment. Also called radiography.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

February, 2024

File name	Version	Contains confidential information	Date
Clarification Questions	V1.0	Yes	19 March 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A 1. Priority question. The External Assessment Group (EAG) noticed an omission in the line for disease stage from both the clinical and costs searches, example from clinical effectiveness Embase strategy (Appendix D, Table 3.):

[#10] ((early* adj2 cancer) or early stage or locally advanc* or stage 1a* or stage Ia* or stage 1b* or stage Ib* or stage 2* or stage II* or stage 3* or stage I-II*).ab,ti,kf.

The terms Stage 1 or Stage I appear to be missing. The EAG reran the Embase search to see what impact this may have had on the overall recall of results, with the addition of these two additional terms the overall recall increased from 3296 (on EAG date of searching 20.2.24) to 3569. Please could the company rerun the affected searches with the additional terms and screen any results not retrieved by the original searches to ensure that no relevant papers have been missed.

Response

Database searches to identify clinical evidence were rerun on 6th March 2024 in which the terms ‘stage 1’ and ‘stage I’ were included in the search strategies (see Table 1, Table 2, Table 3, and Table 4).

In total, there were 7,844 hits from these database searches, and after de-duplication between databases and versus the previously conducted searches, 870 articles were reviewed.

The majority of articles did not meet the eligibility criteria for inclusion and full extraction (i.e. randomised-controlled trials [RCTs], excluding trials comparing between different surgery regimens) based on title/abstract review. The only potentially relevant (RCT) articles that were identified from the review included:

1. Additional publications for the NEOpredict, Altorki 2021 and NEOSTAR studies, none of which were relevant for the ITC[1-3]

2. A secondary publication for the PEARLS/KEYNOTE-091 trial (from the ESMO-IO congress in December 2023, and therefore not identified in the clinical TLR update), which would not be relevant for inclusion in the SLR, but would be relevant for inclusion in the TLR of adjuvant IO studies[4]

3. Two articles from two new studies, neither of which would have been relevant for the ITC as they do not include a neoadjuvant chemotherapy arm, and do not include an intervention arm that is of interest for the decision problem:

    3.1. Chang et al. 2015 reported a pooled analysis of two RCTs comparing stereotactic ablative radiotherapy (SABR) versus surgery in patients with operable, stage I NSCLC[5]

    3.2. Ishii et al. 1994 compared adjuvant OK-432 + chemotherapy versus adjuvant chemotherapy alone in patients undergoing surgical resection[6]

Therefore, no new RCTs or new articles from existing RCTs were identified from these updated searches which would have been considered relevant for the EFS ITC.

Furthermore, a comparison of studies included in the Company Submission (CS) networks versus TA876 has been provided below in order to demonstrate that there are no missing relevant studies. The list of studies ultimately considered for and included in the networks of evidence for the event-free survival (EFS) indirect treatment comparisons (Appendix D.1.2.4) are similar to those included in the networks of evidence in TA876 (excluding AEGEAN and neoadjuvant chemoradiotherapy [CRT] studies), based on the information provided in the Company Evidence Submission of TA876 (page 63 of the Committee Papers) (Table 5).

Searches for evidence on costs and healthcare resource use were not rerun, with the review of clinical evidence prioritised for this response. The healthcare resource use-related inputs used in the model (e.g. for disease management costs) were based on those which have been used in recent NICE appraisals for therapies in resectable NSCLC.

Table 1. Search terms for use in MEDLINE (searched via the Ovid SP platform)

Term group	#	Search terms	Original SLR Hits: 27/07/2022	SLR Update Hits: 30/10/2023	SLR correction hits: 06/03/24

Resectable Stage I-III NSCLC	-	**exp carcinoma, non-small-cell lung/**	**65988**	**71714**	**73708**
	-	NSCLC.ti,ab,kf.	55433	61966	64008
	-	1 or 2	82147	90524	93167
	-	exp Lung Neoplasms/	264036	277449	282225
	-	((lung or pulmonary) adj3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)).ti,ab,kf.	268284	290971	298205
	-	4 or 5	357132	381810	389665
	-	(non small or nonsmall).ti,ab,kf.	83028	91341	93969
	-	6 and 7	82326	90590	93197
	-	3 or 8	95603	104966	107951
	-	((early* adj2 cancer) or early stage or locally advanc* or stage 1* or stage I* or stage 1a* or stage Ia* or stage 1b* or stage Ib* or stage 2* or stage II* or stage 3* or stage I-II*).ab,ti,kf.	265402	288092	390237
	-	Surgical procedures, operative/	56765	56880	56917
	-	(lung* or pulmon* or bronchi* or thora*)	1749230	1839191	1866962
	-	11 and 12	4110	4113	4112
	-	Neoadjuvant therapy/ or pulmonary surgical procedures/ or pneumonectomy/	57945	61167	62161
	-	(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*).ti,ab,kf.	3316560	3556724	3628983
	-	13 or 14 or 15	3323732	3563997	3636273
	-	9 and 10 and 16	7652	8466	10612
RCTs and non-RCTs	-	Randomized Controlled Trials as Topic/	157425	164546	167254
	-	Randomized Controlled Trial/	575635	601408	609654
	-	Random Allocation/	106871	107032	107026
	-	Double-Blind Method/	172836	176377	177656
	-	Single-Blind Method/	32155	32987	33294
	-	Placebos/	35921	35933	35931
	-	exp Clinical Trials as Topic/	376634	385219	388523
	-	Clinical Trial/	535962	538884	539576
	-	Clinical Trial, Phase I/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/	78015	81854	83222
	-	Controlled Clinical Trial/ or Adaptive Clinical Trial/	95026	95461	95608
	-	randomized controlled trial.pt.	575635	601408	609654
	-	clinical trial.pt.	535962	538884	539576
	-	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	78015	81854	83222
	-	(controlled clinical trial or multicenter study).pt.	416181	430561	435445
	-	(clinical adj trial*).ti,ab,kf.	457314	503782	518439
	-	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).ti,ab,kf.	190800	200365	203573
	-	Placebo*.ti,ab,kf.	239375	251365	255193
	-	(allocat* adj2 random*).ti,ab,kf.	41297	44736	45852
	-	(Randomi?ed adj2 trial*).ti,ab,kf.	397815	441437	455335

	-	rct.ti,ab,kf.	30770	35316	36693
	-	(single arm adj3 (trial* or stud*)).ti,ab,kf.	8037	9764	10311
	-	(open label adj (trial* or stud*)).ti,ab,kf.	12856	13682	13942
	-	(non blinded adj (trial* or stud*)).ti,ab,kf.	222	238	244
	-	(pragmatic trial* or pragmatic stud*).ti,ab,kf.	2333	2673	2777
	-	pragmatic clinical trial/	2137	2254	2329
	-	or/18-42	1960995	2068396	2102432
Exclusion	-	exp animals/ not exp humans/	5040396	5163641	5200123
	-	(comment or editorial or case reports or historical article).pt.	4010722	4181589	4227437
	-	(case stud* or case report*).ti.	353229	391770	403513
	-	or/44-46	9041286	9340455	9424214
Combination	-	17 and 43	2014	2175	2557
	-	48 not 47	1,970	2,121	2497

Note: Yellow highlighting denotes updates to search strategy

Database(s): Original SLR: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to July 26, 2022. SLR update: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to October 27, 2023. SLR Correction: Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations March 04, 2024

Abbreviations: NSCLC: non-small cell lung cancer; RCT: randomised controlled trial; SLR: systematic literature review.

Table 2. Search terms for use in Embase (searched via the Ovid SP platform)

Term group	#	Search terms	Original SLR Hits: 27/07/2022	SLR Update Hits: 30/10/2023	SLR correction 06/03/24
Resectable Stage I-III NSCLC		exp non small cell lung cancer/	132388	156582	164166
		NSCLC.ti,ab,kf.	100397	112695	116695
		1 or 2	169720	194614	202323
		exp lung tumor/	437805	485529	500131
		((lung or pulmonary) adj3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)).ti,ab,kf.	385155	422544	434638
		4 or 5	537846	591145	607346
		(non small or nonsmall).ti,ab,kf.	129949	144243	148929
		6 and 7	128710	142923	147574
		3 or 8	194593	220378	228283
		((early* adj2 cancer) or early stage or locally advanc* or stage 1* or stage I* or stage 1a* or stage Ia* or stage 1b* or stage Ib* or stage 2* or stage II* or stage 3* or stage I-II*).ab,ti,kf.	423544	464378	616037
		Surgical procedures, operative/	603394	723035	748480
		(lung* or pulmon* or bronchi* or thora*)	2618164	2835187	2898342
		11 and 12	84474	102135	106892
		lung resection/ or lung surgery/ or neoadjuvant therapy/	57572	63066	64347
		(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or	4268223	4618327	4721688

		pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*).ti,ab,kf.			
		13 or 14 or 15	4286150	4644251	4749164
		9 and 10 and 16	15190	16986	21551
RCTs and non-RCTs		"randomized controlled trial (topic)"/	232600	264210	269906
		randomized controlled trial/	719400	788248	810035
		randomization/	94466	98729	99040
		double blind procedure/	197011	211696	216511
		single blind procedure/	46988	52126	53820
		crossover procedure/	70998	75630	77157
		placebo/	383755	403802	409756
		exp "clinical trial (topic)"/	398961	447636	456941
		clinical trial/	1039596	1072593	1079612
		phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	198592	221450	232132
		controlled clinical trial/ or adaptive clinical trial/ or multicenter study/	734470	783636	795320
		(clinical adj trial*).ti,ab,kf.	656580	728264	751016
		((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).ti,ab,kf.	266188	283068	288133
		Placebo*.ti,ab,kf.	347755	369739	376535
		(allocat* adj2 random*).ti,ab,kf.	50911	55447	56793
		(Randomi?ed adj2 trial*).ti,ab,kf.	534259	592653	610557
		rct.ti,ab,kf.	50933	57866	59941
		(single arm adj3 (trial* or stud*)).ti,ab,kf.	16405	19861	21175
		(open label adj (trial* or stud*)).ti,ab,kf.	22746	24622	25295
		(non blinded adj (trial* or stud*)).ti,ab,kf.	325	348	355
		(pragmatic trial* or pragmatic stud*).ti,ab,kf.	3148	3694	3837
		pragmatic trial/	1723	2367	2567
		or/18-39	2756228	2984793	3050099
Exclusion		("conference abstract" or "conference review").pt.	4478313	4941372	5086246
		limit 41 to yr="1974-2019"	3827598	3864902	3871498
		exp animals/ not exp humans/	4976023	5155468	5217688
		editorial.pt.	732301	782894	797091
		editorial/ or case report/	3460114	3672992	3731622
		(case stud* or case report*).ti.	428308	473718	487432
		or/42-46	11787521	12220334	12348874
Combination		17 and 40	4075	4616	5460
		48 not 47	**2,621**	**3,118**	**3,700**

Note: Yellow highlighting denotes updates to search strategy

Database(s): Original SLR: Embase 1974 to 26 July 2022. SLR update: Embase 1974 to 27 October 2023. SLR correction: Embase 1974 to 2024 March 04

Abbreviations: NSCLC: non-small cell lung cancer; RCT: randomised controlled trial; SLR: systematic literature review.

Table 3. Search terms for use in the Cochrane Library databases (searched simultaneously via the Wiley platform)

Term group	#	Search terms	Original SLR Hits: 27/07/2022	SLR Update Hits: 30/10/2023	SLR Correction 06/03/24
Resectable Stage I-III NSCLC	a)	[mh "carcinoma, non-small-cell lung"]	4828	5839	6577
	b)	NSCLC:ab,ti,kw	10403	11377	11860
	c)	#1 or #2	12136	13457	14131
	d)	[mh "Lung Neoplasms"]	8631	10548	11959
	e)	((lung or pulmonary) NEAR/3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)):ab,ti,kw	25311	27754	28802
	f)	#4 or #5	25583	28062	29146
	g)	(non small or nonsmall):ab,ti,kw	30427	33237	33852
	h)	#6 and #7	15014	16314	16911
	i)	#3 or #8	15694	17036	17651
	j)	((early* NEAR/2 cancer) or "early stage" or locally NEXT advanc* or stage NEXT 1* or stage NEXT I* or stage NEXT 1a* or stage NEXT Ia* or stage NEXT 1b* or stage NEXT Ib* or stage NEXT 2* or stage NEXT II* or stage NEXT 3* or stage NEXT I-II*):ab,ti,kw	44926	49792	61806
	k)	[mh ^"Surgical procedures, operative"]	1079	1278	1404
	l)	(lung* or pulmon* or bronchi* or thora*)	153153	149801	171886
	m)	#11 and #12	135	138	176
	n)	[mh ^Pneumonectomy] or [mh ^"pulmonary surgical procedures"] or [mh ^"neoadjuvant therapy"]	2057	3154	3491
	o)	(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*):ab,ti,kw	331264	374906	390553
	p)	#13 or #14 or #15	331264	374906	390553
	q)	#9 and #10 and #16	1969	2209	2616
RCTS and non-RCTs	r)	[mh ^"Randomized Controlled Trials as Topic"]	12812	42547	51740
	s)	[mh ^"Randomized Controlled Trial"]	118	25732	37
	t)	[mh ^"Random Allocation"]	20678	23366	26018
	u)	[mh ^"Double-Blind Method"]	147701	155271	170112
	v)	[mh ^"Single-Blind Method"]	23070	24682	27179
	w)	[mh ^Placebos]	24595	25630	27185
	x)	[mh "Clinical Trials as Topic"]	48709	84414	95888
	y)	[mh ^"Clinical Trial"]	29	19265	10
	z)	[mh ^"Clinical Trial, Phase I"] or [mh ^"Clinical Trial, Phase II"] or [mh ^"Clinical Trial, Phase III"] or [mh ^"Clinical Trial, Phase IV"]	0	0	0
	aa	[mh ^"Controlled Clinical Trial"] or [mh ^"Adaptive Clinical Trial"]	31	17160	7
	bb	"randomized controlled trial":pt	556044	0	0
	cc	"clinical trial":pt	333860	19093	0

	dd	("clinical trial, phase i" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv"):pt	35912	0	0
	ee	("controlled clinical trial" or "multicenter study"):pt	183921	0	0
	ff)	(clinical NEXT trial*):ab,ti,kw	476796	526142	549038
	gg	((singl* or doubl* or treb* or tripl*) NEXT (blind* or mask*)):ab,ti,kw	375874	402158	417852
	hh	Placebo*:ab,ti,kw	346204	372468	383767
	ii)	(allocat* NEAR/2 random*):ab,ti,kw	70036	78257	83520
	jj)	(Randomi?ed NEAR/2 trial*):ab,ti,kw	683244	756473	792292
	kk	rct:ab,ti,kw	33999	39257	39906
	ll)	("single arm" NEAR/3 (trial* or stud*)):ab,ti,kw	2609	2942	3120
	mm	("open label" NEXT (trial* or stud*)):ab,ti,kw	11511	12479	12955
	nn	("non blinded" NEXT (trial* or stud*)):ab,ti,kw	241	267	278
	oo	(pragmatic NEXT trial* or pragmatic NEXT stud*):ab,ti,kw	2245	2606	2798
	pp	[mh ^"pragmatic clinical trial"]	0	0	0
	qq	{or #18-#42}	1321655	1220127	1254922
Combination	rr)	#17 and #43	1302	1336	1602
	ss	#44 in Cochrane Reviews	**9**	**9**	**10**
	tt)	#44 in Trials	**1,293**	**1,327**	**1,592**

Database(s): Original SLR: Cochrane Database of Systematic Reviews, Issue 7 of 12, July 2022; Cochrane Central Register of Controlled Trials, Issue 7 of 12, July 2022. SLR update: Cochrane Database of Systematic Reviews, Issue 10 of 12, October 2023; Cochrane Central Register of Controlled Trials, Issue 10 of 12, October 2023. SLR correction: CDSR, Issue 3 of 12, March 2024; CENTRAL Issue 2 of 12, February 2024

Table 4. Search terms for the DARE database (searched via the York CRD platform)

Term group	#	Search terms	Hits: 27/07/2022	Hits: 06/03/24
Resectable Stage I-III NSCLC		MeSH DESCRIPTOR carcinoma, non-small-cell lung EXPLODE ALL TREES	668	668
		(NSCLC)	257	257
		#1 or #2	732	732
		MeSH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES	1151	1151
		((lung or pulmonary) adj2 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)) or ((cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous) adj2 (lung or pulmonary))	1451	1451
		#4 or #5	1465	1465
		((non small or nonsmall))	821	821
		#6 and #7	819	819
		#3 or #8	833	833
		(early* adj1 cancer) or (cancer adj1 early*)	329	329
		("early stage" or "locally advanc*" or "stage 1*" or "stage I*" or "stage 1a*" or "stage Ia*" or "stage 1b*" or "stage Ib*" or "stage 2*" or "stage II*" or "stage 3*" or "stage I-II*")	1218	1511
		#10 or #11	1453	1736
		MeSH DESCRIPTOR Surgical procedures, operative	243	243
		(lung* or pulmon* or bronchi* or thora*)	6060	6060
		#13 and #14	25	25
		MeSH DESCRIPTOR Pneumonectomy	103	103
		MeSH DESCRIPTOR pulmonary surgical procedures	4	4
		MeSH DESCRIPTOR neoadjuvant therapy	175	175
		(neoadjuvant* or neo-adjuvant* or resect* or surg* or lobectom* or segmentectom* or pneumonectom* or bilobectom* or preop* or pre-op* or operable* or operat*)	19544	19544
		#15 or #16 or #17 or #18 or #19	19544	19544
		#9 and #12 and #20	58	84
Combination		#21 in DARE	**34**	**45**

Note: Yellow highlighting denotes updates to search strategy

Database(s): Database of Abstracts of Reviews of Effect: Issue 2 of 4, April 2015. SLR update: DARE was not searched as the database has not been updated since the original SLR.

Table 5. Comparisons of studies included in ID6220 and TA876 networks

Study name (Author Year)	Inclusion in ID6220 networks	Inclusion in TA876 networks
Interventions of interest:	Adjuvant chemotherapy, neoadjuvant chemotherapy, neoadjuvant nivolumab + PDC, surgery only, perioperative durvalumab + neoadjuvant PDC	Adjuvant chemotherapy, neoadjuvant chemotherapy, neoadjuvant nivolumab + PDC, surgery only, neoadjuvant CRT
CheckMate 816 (Forde 2022)[7]	Yes	Yes

NATCH (Felip 2010)[8]	Yes	Yes
Chen 2013[9]	Considered in feasibility assessment, but excluded due to availability of EFS HRs	Yes, in sensitivity analysis including 2G chemotherapy
CHEST (Scagliotti 2012)[10]	Yes	Yes
Depierre 2002[11]	Considered in feasibility assessment, but excluded due to availability of EFS HRs	Yes, in sensitivity analysis including 2G chemotherapy
JCOG 9209 (Nagai 2003)[12]	Considered in feasibility assessment, but excluded due to availability of EFS HRs	Yes, in sensitivity analysis including 2G chemotherapy
Li 2009[13]	Yes	Yes
MRC LU22/NVALT 2/EORTC 08012 (Gilligan 2007)[14]	Yes	Yes, in sensitivity analysis including 2G chemotherapy
Rosell 1994[15]	Yes	Yes, in sensitivity analysis including 2G chemotherapy
Roth 1994[16]	Considered in feasibility assessment, but excluded due to availability of EFS HRs	No
SWOG S9900 (Pisters 2010)[17]	Yes	Yes
Additional studies:		
AEGEAN (Heymach 2023)[18]	Yes	No, not relevant comparator
SAKK 16/00 SWS-SAKK-16/00 EU-20138 (Pless 2015)[19]	No, neoadjuvant CRT study	Yes
WJTOG9903 (Katakami 2012)[20]		Yes
IFCT-0101 (Girard 2010)[21]		Yes
JBR-10 (Butts 2010)[22]	No, study population is completely resected and EFS not reported	Yes, in sensitivity analysis including completely resected patients
ANITA (Douillard 2006)[23]		
Ou 2010[24]		
CALGB 9633 (Straus 2008)[25]		

Abbreviations: 2G, second generation; CRT, chemoradiotherapy; EFS, event-free survival; HR, hazard ratio; PDC, platinum-doublet chemotherapy

A 2. The searches strategies reported for Appendix D (Identification, selection, and synthesis of clinical evidence) are missing line numbers, please provide corrected tables in order to make them more transparent.

Response

The line numbers (labelled search numbers) are reported for all search strategies in Appendix D.

A 3. Please confirm whether any additional searches, other than those reported in Appendix D section D.1, were conducted to retrieve information regarding adverse events (AEs) for durvalumab and, if so, provide full details including date, resource names and search strategies used.

Response

No additional searches were conducted to retrieve information regarding AEs for durvalumab.

Adverse events were included as an outcome of interest in the systematic literature review (SLR) (as described in Appendix D). Additional information on the safety profile of durvalumab (as monotherapy or in combination with chemotherapy) from across other approved indications can be found in the Summary of Product Characteristics in Appendix C. As described in Section B.2.10, the safety profile of durvalumab (in combination with neoadjuvant platinum-doublet chemotherapy [PDC] and as monotherapy following surgery) in the AEGEAN trial was consistent with the known safety profile for durvalumab and chemotherapy agents.

A 4. In Appendix D the search of the two Cochrane library resources (CDSR and CENTRAL) carries a randomised controlled trial (RCT) study design filter which is against best practice as these are prefiltered resources. Please explain the rationale behind this and what impact it may have had on the recall of results.

The search strategy for the Cochrane library resources used the prespecified filters for RCT study design. This was a pragmatic choice, designed to improve the specificity of the searches.

It is not expected that the inclusion/exclusion of the prespecified filter will have had a material impact on the RCTs that were included in the evidence networks for indirect treatment comparisons (ITC)s, when compared to the list of RCTs included in the network for TA876 (see response to A1; Table 5).

A 5. The Evidence Assessment Group (EAG) noted that there appears to be two potential errors in the reporting of the Cochrane strategy:

a) Line #43 contains the terms: “4-#42” This is not correct syntax for this resource and retrieves an error message and the numbers selected don’t appear to make sense as a line combination, please can you confirm if this is a reporting error and provide the original strategy as run.

b) The EAG also noted that the update search for Line #45 only retrieved 1 record, whereas the original search reported 9. Appendix D, Section D.1.1 stated that *“For the update, no date restrictions were imposed; instead, the results of the updated searches were de-duplicated against those of the original searches.”* Is this a reporting error? (please note that this number is also reported in the PRISMA flowchart (Appendix D, Section D.1.2).

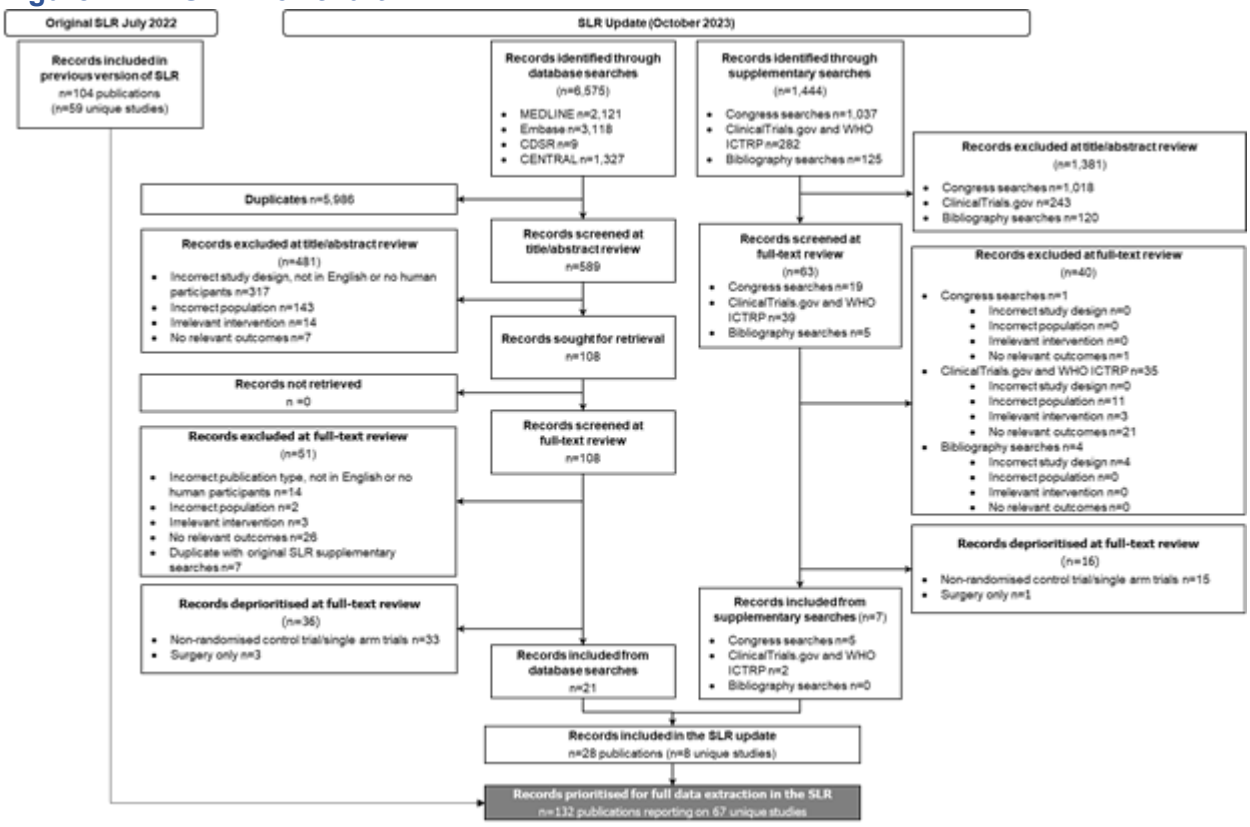
Response

a) The terms in line #43 are reported in error. The correct terms are #16-#42.

b) This was a reporting error. A total of 9 hits were identified in the updated search (30/10/2023) and this should have been reported in line #45.

In the PRISMA flowchart (Figure 1), search results from the Cochrane database were erroneously added to the number of CENTRAL search results. The search results in the PRISMA should be: CDSR, n=9 and CENTRAL, n=1,327. The updated PRISMA is provided below.

Figure 1. PRISMA flowchart



Abbreviations: SLR, systematic literature review

A 6. Appendix G mentioned searches of grey literature resources CEA (cost-effectiveness analysis) registry, ScHARRHUD (ScHARR Health Utilities Database), EQ5D (EuroQol Health-Related Quality of Life measure) publications database and the websites of individual country specific HTA (Health Technology Assessment) bodies. However, no information as to search terms or hits per resource is reported. Please provide full details for each resource including date searched. The EAG presumes that these searches were also used to inform both Appendix H: HRQoL and Appendix I: Resource use. Please confirm if this is the case.

Response:

The resources searched, search terms used, number of hits, and number of included studies are presented in Table 6 for the CEA, ScHARRHUD, and EQ5D searches, and in Table 7 for the search of HTA bodies. The grey literature searches informed the SLR for cost-effectiveness studies as well as the SLRs for HRQoL studies and resource use studies.

Table 6. Search strategies for hand-searching of grey literature registries

Registry	Link	Search strategy	September 14th 2023		November 27th 2023	
			Hits	Included	Hits	Included
The Cost-effectiveness Analysis (CEA) Registry	Tufts CEA – Tufts CEA (tuftsmedicalcenter.org)	1) resectable AND NSCLC	1	0	0	0
		2) operable AND NSCLC	6	0	0	0
		3) neo-adjuvant AND NSCLC	0	0	0	0
		4) neoadjuvant AND NSCLC	1	0	0	0
		5) adjuvant AND NSCLC	4	0	0	0
		6) resected AND NSCLC	1	0	0	0
		7) surgery AND NSCLC	8	0	0	0
		8) resectable AND non-small cell lung cancer	1	0	0	0
		9) operable AND non-small cell lung cancer	6	0	0	0
		10) neo-adjuvant AND non-small cell lung cancer	0	0	0	0
		11) neoadjuvant AND non-small cell lung cancer	1	0	0	0
		12) adjuvant AND non-small cell lung cancer	8	0	0	0
		13) resected AND non-small cell lung cancer	2	0	0	0
		14) surgery AND non-small cell lung cancer	12	0	0	0

The EQ-5D Publications Database	http://eq-5dpublications.euroqol.org/?noheader=true	NSCLC + cost NSCLC + economic NSCLC + utility NSCLC + utilities NSCLC + quality of life NSCLC + resource Non-small cell lung cancer + cost Non-small cell lung cancer + economic Non-small cell lung cancer + utility Non-small cell lung cancer + utilities Non-small cell lung cancer + quality of life Non-small cell lung cancer + resource	0 0 0 0 0 0 0 0 0 0 0 0	0 0 0 0 0 0 0 0 0 0 0 0	0 0 0 0 0 0 0 0 0 0 0 0	0 0 0 0 0 0 0 0 0 0 0 0
The School of Health and Related Research Health Utilities Database (ScHARRHUD), University of Sheffield	http://www.scharrhud.org/	NSCLC OR non-small cell lung cancer OR non small cell lung cancer	5	0	0	0

Table 7. Search strategies for hand-searching of relevant HTA bodies

Source	Link	Search strategy	September 14th 2023			November 27th 2023		
			Hits	Reviewed	Included	Hits	Reviewed	Included

PBAC	https://pbac.pbs.gov.au/	NSCLC non-small cell lung cancer non small cell lung cancer	64 95 149	3 0 0	1 0 0	NA	NA	NA
PBAC	https://pbac.pbs.gov.au/	Nivolumab atezolizumab Osimertinib	112 67 20	0 2 0	0 1 0	2 0 0	2 0 0	1 0 0
CADTH	https://www.cadth.ca/node/8	NSCLC non-small cell lung cancer non small cell lung cancer	12 16 18	9 2 0	2 0 0	3 2 2	3 2 2	0 0 0
NICE	https://www.nice.org.uk/	NSCLC non-small cell lung cancer non small cell lung cancer	8 13 13	2 0 0	2 0 0	0 0 0	0 0 0	0 0 0
HAS	https ://www.has-sante.fr/	NSCLC non-small cell lung cancer	8 13	2 2	0 0	0 1	0 1	0 1
IQWiG	https://www.iqwig.de/en/	NSCLC non-small cell lung cancer	14 4	14 4	0 0	0 0	0 0	0 0
AGENAS	https://www.agenas.gov.it/	NSCLC non-small cell lung cancer	1 1	1 1	0 0	0 0	0 0	0 0
NCPE	http://www.ncpe.ie/	NSCLC non-small cell lung cancer	16 22	7 12	1 1	0 0	0 0	0 0
SMC	https://www.scottishmedicines.org.uk/	NSCLC non-small cell lung cancer	3 3	0 0	0 0	0 0	0 0	0 0
AEMPS	https://www.aemps.gob.es/?lang=en	NSCLC non-small cell lung cancer	0 3	0 0	0 0	0 0	0 0	0 0
AWMSG	https://awmsg.nhs.wales/	NSCLC non-small cell lung cancer	0 295	0 0	0 0	0 0	0 0	0 0

Decision problem

A 7. Priority question. The omission of the comparator neoadjuvant chemoradiotherapy from the decision problem appears to be based on only clinical opinion, whereas National Institute for Health and Care Excellence (NICE) guideline 122 (NG122) recommends surgery, radiotherapy, chemoradiotherapy or a combination of these for stage 1 to 2 non-small-cell lung cancer (NSCLC).

a) Please provide data that demonstrates lack of neoadjuvant chemoradiotherapy use in clinical practice.

b) If omission cannot be justified, please include this comparator in the decision problem and therefore in all comparative clinical and cost effectiveness analyses.

Response

Although neoadjuvant CRT is recommended in NG122[26] for stage IIIA-N2 patients, this is a small subset of patients equating to roughly 7% of NSCLC patients, which are not typically considered resectable. Duan et al, 2020[27] demonstrates that the population of patients eligible for neoadjuvant CRT is only about 7% of NSCLC patients and Adizie et al, 2019[28] reported CRT being administered in only 5% of stage IIIA NSCLC patients in England. Clinicians in attendance at the 2024 UK advisory board[29] unanimously agreed that neoadjuvant CRT is not offered to patients with resectable NSCLC in UK clinical practice. This is further supported by clinical expert opinion gathered for TA876[30], where neoadjuvant CRT was described as typically being reserved for patients considered to be unresectable. As such, neoadjuvant CRT is not a comparator of interest for this appraisal and is therefore appropriately excluded from comparative clinical and cost-effectiveness analyses.

A 8. Surgery alone is taken by the company to represent active monitoring. It is unclear if this means that surgery alone will always be accompanied by active monitoring, whether surgery itself is deemed a type of active monitoring, or both. In any event, there are more forms of active monitoring

than surgery, and these seem to be excluded. Please clarify what is meant by *"Surgery alone is assumed to represent active monitoring"*.

Response

Surgery alone is deemed to represent a type of active monitoring in resectable patients. It is considered the only relevant representation of active monitoring where no systemic anticancer therapy is given. This approach is consistent with the company submission for TA876.[30]

Systematic review

A 9. The company stated that "in total across the original SLR and SLR update 132 publications reporting on 67 unique RCTs were prioritised for full data extraction." Additionally, the company also stated, "Following the implementation of the evidence prioritisation strategy, which prioritised evidence from RCTs and deprioritised evidence from trials comparing surgery alone treatment arms, 258 (36 update) records were deprioritised, leaving 69 (21 update) articles ultimately undergoing full data extraction". Whereas, in Table 13 of the appendices (Appendix D) of the CS, 68 RCTs were presented. Please clarify the discrepancy on whether 67, 68 or 69 RCTs were included.

Response

The statement that "in total across the original SLR and SLR update 132 publications reporting on 67 unique RCTs were prioritised for full data extraction" is correct. This is consistent with the PRISMA in Appendix D.1.2.

The inclusion of 68 unique studies in Table 13 of Appendix D is an error. This is due to the incorrect inclusion of the Lei 2020[31] article (NCT04338620) as a unique study. This article reports from the TD-FOREKNOW study, for which additional publications were identified as part of the updated SLR searches (see Lei 2023[32] as the primary publication for TD-FOREKNOW, which also refers to NCT04338620). When including Lei 2020[31] as a secondary publication for the TD-FOREKNOW study, the number of unique studies is 67.

The statement "…leaving 69 (21 update) articles ultimately undergoing full data extraction" refers to the number of articles that were included in the full data extraction during the original SLR searches. This is therefore referring to a different value to the number of unique RCTs identified across both original and updated SLR searches.

Clinical effectiveness evidence

A 10. Priority question. In the AEGEAN trial, the most recent data cut-off (DCO) for clinical efficacy outcomes was November 2022, despite this being over 15 months ago.

a) Please explain why a more recent DCO was not used.

b) Provide data for a more recent DCO if possible

c) Redo all analyses (including the indirect treatment comparisons (ITCs) and health economic analyses) using these more recent data

Response

The 10 November 2022 DCO is the most recent planned analysis for the AEGEAN trial following multiple testing procedure (MTP). As stated in the CS, a safety update was provided to the US Food and Drug Administration (FDA) review as part of regulatory procedures (DCO [redacted]). It was agreed with the FDA that overall survival (OS) would be unblinded and provided at the time of the safety update to support benefit-risk assessment. The day 120 safety update (D120SU), therefore, is limited to safety outcomes and overall survival. A second planned interim analysis containing a more extensive set of outcomes is expected to become available later in 2024, when EFS data is at approximately 40% maturity.

A 11. The baseline characteristics comprise the whole randomised cohort of the AEGEAN trial, but this does not necessarily represent the patients for whom outcome data are reported in the primary and final data cut-off points. It is therefore difficult to estimate the risk of random selection bias on the reported outcomes. Please provide the baseline characteristics for the

patients participating in the specific data cut-off points relating to the reported outcome data.

Response

Baseline characteristics for the modified intent-to-treat (mITT) are presented in the CS. The mITT population included all randomised patients, excluding those whose tumours have known epidermal growth factor receptor mutations (EGFRm) or anaplastic lymphoma kinase (ALK) gene rearrangements. Unless otherwise specified, the mITT population or subsets of the mITT population were used for all efficacy analyses, including patient-reported outcomes (PROs). Treatment arms were compared on the basis of randomised study treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment were included in the analysis in the treatment arm to which they were randomised.

The baseline characteristics presented for outcomes at the first interim analysis (IA1) of EFS, therefore, are the same as those for whom outcome data are reported at the D120SU. The only discrepancy in baseline characteristics for presented outcomes is for the 14 January 2022 DCO, where pathological complete response (pCR) was analysed, as not all patients had been randomised at this point in time. This analysis was planned to be conducted after approximately 400 patients in the mITT population had a minimum opportunity for follow-up of approximately 7 months prior to DCO in order to allow time for surgery and pCR assessment by a central pathology laboratory to occur (interim ITT cohort). The baseline patient and disease characteristics for the mITT population at EFS IA1, the D120SU, and pCR IA1 are presented in Table 8 and Table 9.

Table 8. Baseline patient characteristics in AEGEAN, mITT population at EFS IA1, D120SU, and pCR IA1

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	Perioperative placebo n=374	Perioperative durvalumab n=366	Perioperative placebo n=374	Perioperative durvalumab n=196	Perioperative placebo n=206
Median age, years (range)	65 (30–88)	65 (39–85)	65 (30–88)	65 (39–85)	[redacted]	[redacted]
≥75 years, n (%)	44 (12.0)	36 (9.6)	44 (12.0)	36 (9.6)	[redacted]	[redacted]
Characteristic	252 (68.9)	278 (74.3)	252 (68.9)	278 (74.3)	[redacted]	[redacted]
Race, n (%)						
Asian	143 (39.1)	164 (43.9)	143 (39.1)	164 (43.9)	[redacted]	[redacted]
White	206 (56.3)	191 (51.1)	206 (56.3)	191 (51.1)	[redacted]	[redacted]
Other	17 (4.6)	19 (5.1)	17 (4.6)	19 (5.1)		
Region, n (%)						
Asia	142 (38.8)	163 (43.6)	142 (38.8)	163 (43.6)	[redacted]	[redacted]
Europe	141 (38.5)	140 (37.4)	141 (38.5)	140 (37.4)	[redacted]	[redacted]
North America	43 (11.7)	43 (11.5)	43 (11.7)	43 (11.5)	[redacted]	[redacted]
South America	40 (10.9)	28 (7.5)	40 (10.9)	28 (7.5)	[redacted]	[redacted]
Smoking status, n (%)						
Never	51 (13.9)	56 (15.0)	51 (13.9)	56 (15.0)	[redacted]	[redacted]
Former	220 (60.1)	223 (59.6)	220 (60.1)	223 (59.6)	[redacted]	[redacted]
Current	95 (26.0)	95 (25.4)	95 (26.0)	95 (25.4)	[redacted]	[redacted]

Abbreviations: D120SU, day 120 safety update; EFS, event-free survival; IA1, interim analysis 1; mITT, modified intent-to-treat; NR, not reported; pCR, pathological complete response

Source: AstraZeneca 2023[33]

Table 9. Baseline disease characteristics in AEGEAN, mITT population at EFS IA1, D120SU, and pCR IA1

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	Perioperative placebo n=374	Perioperative durvalumab n=366	Perioperative placebo n=374	Perioperative durvalumab n=196	Perioperative placebo n=206
ECOG performance status, n (%)						
0	251 (68.6)	255 (68.2)	251 (68.6)	255 (68.2)	[redacted]	[redacted]
1	115 (31.4)	119 (31.8)	115 (31.4)	119 (31.8)	[redacted]	[redacted]
AJCC stage[a] at diagnosis, n (%)						
II	104 (28.4)	110 (29.4)	104 (28.4)	110 (29.4)	[redacted]	[redacted]
IIIA	173 (47.3)	165 (44.1)	173 (47.3)	165 (44.1)	[redacted]	[redacted]
IIIB	88 (24.0)	98 (26.2)	88 (24.0)	98 (26.2)	[redacted]	[redacted]
Histology type, n (%)						
Squamous	169 (46.2)	191 (51.1)	169 (46.2)	191 (51.1)	[redacted]	[redacted]
Non-squamous	196 (53.6)	179 (47.9)	196 (53.6)	179 (47.9)	[redacted]	[redacted]

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	Perioperative placebo n=374	Perioperative durvalumab n=366	Perioperative placebo n=374	Perioperative durvalumab n=196	Perioperative placebo n=206
TNM classification						
Primary tumour, n (%)						
T1	44 (12.0)	43 (11.5)	44 (12.0)	43 (11.5)	[redacted]	[redacted]
T2	97 (26.5)	108 (28.9)	97 (26.5)	108 (28.9)	[redacted]	[redacted]
T3	128 (35.0)	129 (34.5)	128 (35.0)	129 (34.5)	[redacted]	[redacted]
T4	97 (26.5)	94 (25.1)	97 (26.5)	94 (25.1)	[redacted]	[redacted]
Regional lymph nodes, n (%)						
N0	110 (30.1)	102 (27.3)	110 (30.1)	102 (27.3)	[redacted]	[redacted]
N1	75 (20.5)	87 (23.3)	75 (20.5)	87 (23.3)	[redacted]	[redacted]
N2	181 (49.5)	185 (49.5)	181 (49.5)	185 (49.5)	[redacted]	[redacted]
PD-L1 expression, n (%)						
TC <1%	122 (33.3)	125 (33.4)	122 (33.3)	125 (33.4)	[redacted]	[redacted]
TC 1-49%	135 (36.9)	142 (38.0)	135 (36.9)	142 (38.0)	[redacted]	[redacted]
TC ≥50%	109 (29.8)	107 (28.6)	109 (29.8)	107 (28.6)	[redacted]	[redacted]
Planned neoadjuvant platinum agent, n (%)						
Cisplatin	100 (27.3)	96 (25.7)	100 (27.3)	96 (25.7)	[redacted]	[redacted]
Carboplatin	266 (72.7)	278 (74.3)	266 (72.7)	278 (74.3)	[redacted]	[redacted]

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand-1; TNM, tumour-node-metastasis

[a] AJCC 8th edition[34]

Source: AstraZeneca 2023[33]

A 12. The company submission (CS) reports that the randomisation method and concealment of treatment allocation in the AEGEAN trial were adequate. However, after reading the published trial report and published trial protocol, levels of selection bias appear to be less satisfactory than reported. Firstly, the precise method of randomisation was unclear; use of the term 'randomised', or stating that 'block randomisation' was used, does not reveal the specific methods of randomisation. Secondly, there was no mention of any method of allocation concealment in the trial report or protocol: certainly, an interactive voice/web recognition system (mentioned in the CS) did not appear to be mentioned in the primary sources. Please provide the documentation that confirms the methodology used for randomisation and for allocation concealment.

Response

The use of an interactive voice/web recognition system (IXRS) is described in the published protocol[35] and its use for the randomisation and allocation concealment is described in more detail in the AEGEAN Clinical Study Report (CSR).[33]

A unique randomization number was then obtained via the IXRS and patients were centrally assigned to one of the 2 treatment arms in a 1:1 ratio. Assignment to durvalumab versus placebo was determined by the randomisation scheme in the IXRS. A blocked randomisation was generated, and all centres used the same list in order to minimise any imbalance in the number of patients assigned to each treatment arm.

A 13. No results are provided for the disease-free survival outcome in the AEGEAN trial, despite being reported by the CS to have been *"formally tested at the primary analysis of EFS* [event-free survival] *(DCO 10 November 2022)"*. The rationale given by the company was that it *"did not meet the prespecified boundary to declare statistically significance"*. This is insufficient rationale for the failure to present an outcome that was prescribed by the NICE scope and agreed to in the decision problem. There appears to be an implication that reporting of this outcome would lead to unblinding, but the mechanism for this is by no means clear.

a) Please give a rationale for why the analysis was not reported.

b) If an adequate rationale is not possible, please present the findings for this outcome.

Response

Disease-free survival (DFS) was tested by the independent data monitoring committee at the primary analysis of EFS (EFS IA1, DCO 10 November 2022) and did not meet the prespecified boundary to declare statistically significant. Therefore, as per the MTP, which consists of a hierarchical gatekeeping strategy, DFS was not reported at EFS IA1 and the study team remain blinded to DFS to preserve the integrity of the outcome. Disease-free survival will be tested when EFS data is at approximately 40% maturity (second interim analysis), in line with the MTP.

A 14. In the AEGEAN trial, results are given at both the primary data analysis point and the final analysis point for the pathological complete response (pCR) and major pathological response (MPR) outcome, whereas they are only given for the primary analysis point for EFS. Please clarify the reasons for this.

Response

As specified in the trial protocol, one interim analysis was planned for pCR, when all patients in the ITT population had the opportunity to undergo surgery (i.e., ~7 months follow-up) and complete central pathology assessment (DCO 14 January 2022). A first interim analysis of EFS was planned to occur when approximately 224 EFS events have occurred (approximately 30% maturity in the mITT). The first interim analysis of EFS coincided with the final analysis of pCR (DCO 10 November 2022). Thus, there was no analysis of EFS at the time of the interim pCR analysis (DCO 14 January 2022).

A 15. No statistical analysis was provided for the objective response rate (ORR) outcome in the AEGEAN trial. Please provide one.

Response

The objective response rate (ORR) is reported in section B.2.6.3.4 of the CS. As stated in the CS, this outcome was evaluated in the mITT population prior to surgery using blinded independent central review (
BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and was not a pre-defined study endpoint. The analysis of ORR was performed on the mITT population using a Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors from IXRS, disease stage (Stage II vs Stage III) and programmed cell death ligand-1 (PD-L1) expression status (tumour cells [TC] < 1% vs TC ≥ 1%). The effect of treatment was estimated by the difference in proportions between treatment arms, together with their corresponding confidence interval (CI) and p-value from the CMH test. The CIs for the difference in proportions between groups was computed using stratified Miettinen and Nurminen's (MN) confidence limits. This analysis was repeated for ORR based on the site investigator assessment. For each treatment arm, the overall visit response from the latest assessment prior to surgery was summarised by n (%) for each category (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD] and not evaluable [NE]).[33]

A 16. For the overall survival (OS) outcome, the company did not undertake a 'formal' analysis in the AEGEAN trial. However, the rationale relating to data maturity and confounding appears weak. Firstly, if the follow up period is so short that the event rate is extremely low, then a full analysis would indeed appear inappropriate, but the proportion dying by the point of cut-off was 22%. This is far higher than the pCR risks at the same data cut-off, which were subject to full analysis. Secondly, the fears of confounding by subsequent therapies are unfounded because there is no reason why the arms should differ in subsequent therapies given the double-blind nature of the study. Given the clear equipoise between arms in the 'immature' OS results, the failure to classify the result as a 'formal' result, without an adequate rationale, suggests bias. Please explain more fully the reasons why OS was not subject to a 'formal' analysis.

Response

The MTP uses a hierarchical, gatekeeping strategy that dictates the testing of OS. The MTP stipulates that OS will not be tested until a positive DFS result. Since DFS did not meet the prespecified boundary to declare statistical significance at EFS IA1, OS was not formally tested for statistical significance.

The OS testing of the DCOs provided in the CS was performed on an ad-hoc basis to support regulatory procedures (see response to A 17. below). Although this testing helps inform the benefit-risk assessment, it does not possess the statistical power of the MTP and therefore cannot be considered part of the formal testing procedure. The sponsor remains blinded to DFS (the gatekeeping outcome for OS), and the study continues in a blinded manner, with patients and investigators blinded as to treatment assignment.

A 17. For the OS outcome from the AEGEAN trial, which yielded a result suggesting the two arms were equivalent at the 10th November 2022 cut-off point, data from the safety-analysis cut-off point at 120 days were used to try to demonstrate intervention efficacy. This is the only clinical outcome where safety-analysis 120 day data were used, which appears to indicate possible bias. Please explain:

a) why the results at 120 days were not used for the other outcomes

b) why it was deemed appropriate to deviate from the primary or final analysis results for this outcome.

Response

The safety analysis was performed as part of the FDA regulatory procedure. This ad-hoc analysis was agreed with the FDA and was limited to safety outcomes and OS. The deviation from MTP for the OS outcome was specifically agreed with the regulatory body to support the benefit-risk assessment as not to delay patient access to treatment whilst further OS data are collected.

A 18. The company has not reported any of the health-related quality of life data in the CS or appendices in the AEGEAN trial. This gives the impression that the company is downplaying the non-significant differences. Certainly, the

lack of the data, with the associated tables and figures, does tend to reduce attention to this outcome. Please provide the quality-of-life data.

Response

The company reported EQ-5D-5L results as these data were deemed the most relevant HRQoL data for this appraisal. Additional PRO/HRQoL data were collected as secondary and exploratory endpoints in the AEGEAN trial. These data are reported below:

Patient-reported outcomes were evaluated in the neoadjuvant period using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC QLQ- Lung Cancer 13 (LC13), as described Appendix N. All PRO/HRQoL data presented here are from the mITT population at the primary analysis of EFS (DCO 10 November 2022).

Overall compliance rates were high at neoadjuvant baseline (> 90% in both arms) for all PRO instruments (EORTC QLQ-C30 and EORTC QLQ-LC13 and EQ-5D-5L). Compliance rates decreased (similarly in both arms) throughout the neoadjuvant period.

Table 10. Compliance with EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L by visit

Timepoint	Compliance	Perioperative durvalumab n=366	Perioperative placebo n=374
EORTC QLQ-C30			
Neoadjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
Neoadjuvant week 12	Expected forms Compliance rate (%)	[redacted]	[redacted]
Adjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
EORTC QLQ-LC13			
Neoadjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
Neoadjuvant week 12	Expected forms Compliance rate (%)	[redacted]	[redacted]
Adjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
EQ-5D-5L			
Neoadjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
Neoadjuvant week 12	Expected forms Compliance rate (%)	[redacted]	[redacted]
Adjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]

*Adjuvant baseline is the latest measurement after surgery but before the 1st adjuvant dose

The PRO/HRQoL data are summarised descriptively with respect to change from baseline and clinically relevant changes. Mixed model for repeated measures (MMRM) were used to estimate changes from baseline and difference between treatment arms, by visit and on average during the neoadjuvant period, with covariate adjustment for baseline score. Assessment of differences between treatment arms was performed descriptively (i.e., no alpha was assigned nor was adjustment made for multiplicity).

EORTC-QLQ-C30 Global measure of health status/quality of life and functioning

For the EORTC-QLQ-C30 Global measure of health status/quality of life (GHS/QoL) and each functional domain there were [redacted] without differences between arms. Most patients in both arms [redacted] report clinically meaningful changes in GHS/QoL or functioning scores.[33] Throughout the neoadjuvant period, the proportion of patients with a clinically meaningful improvement (defined as ≥ 10-point change) in the EORTC-QLQ-C30 global health status/quality of life (GHS/QoL) ranged from [redacted]% to [redacted] % in the durvalumab arm and [redacted] % to [redacted] % in the placebo arm (Week 12 timepoint shown in Table 11).[33] These proportions were generally consistent across visits in the neoadjuvant period and similar across both arms.[33]

Table 11. EORTC QLQ-C30 Global measure of health status/Quality of Life

Timepoint	Measure	Perioperative durvalumab n=366	Perioperative placebo n=374
Change from neoadjuvant baseline			
Neoadjuvant baseline	n Absolute score, mean (SD)	[redacted]	[redacted]
Week 12	n Change from baseline, mean (SD)	[redacted]	[redacted]
Adjuvant baseline*	n Change from baseline, mean (SD)	[redacted]	[redacted]
Clinically relevant changes with respect to neoadjuvant baseline			
Week 12	n Worsened n (%) Improved n (%) Stable n (%)	[redacted]	[redacted]
Adjuvant baseline*	n Worsened n (%) Improved n (%) Stable n (%)	[redacted]	[redacted]

*Adjuvant baseline is the latest measurement after surgery but before the 1st adjuvant dose
Source: AstraZeneca 2023[33]

In the MMRM analysis:

- [redacted] in GHS/QoL, physical functioning and role functioning scores were observed without differences between arms at any visit[33]

EORTC-QLQ-C30 symptom scales

A [redacted] from baseline was observed for all QLQ-C30 symptoms, including fatigue and appetite loss, throughout the neoadjuvant period in both treatment arms.[33] A clinically meaningful (defined as ≥ 10-point change) [redacted] for fatigue was observed at Week 12 in the durvalumab arm (mean change from baseline: [redacted] points versus [redacted] points for the placebo arm).[33]

In the MMRM analysis:

- [redacted] were observed for fatigue with no differences between arms at Week 3, Week 6, and Week 9[33]
- At Week 12, a clinically meaningful (defined as ≥ 10-point change) [redacted] for fatigue was seen for perioperative durvalumab plus neoadjuvant PDC (mean change from baseline: [redacted] points versus [redacted] points for placebo plus chemotherapy)[33]
- The MMRM estimate of the average treatment difference for fatigue considering all neoadjuvant period visits was [redacted] points (95% CI: [redacted] to [redacted])[33]

EORTC-QLQ-LC13

A [redacted] from baseline was observed for coughing throughout the neoadjuvant period in both treatment arms.[33] At the end of the neoadjuvant period (Week 12), a [redacted] from baseline was observed for pain in the chest, with no differences between arms, and a [redacted] from baseline was observed for dyspnoea, pain in other parts, peripheral neuropathy, and alopecia.[33] Only [redacted] changes were observed for pain in arm or shoulder, sore mouth and dysphagia with no differences between treatment arms.[33] Most patients in both arms [redacted] report clinically meaningful changes in coughing, dyspnoea, or pain in the chest.[33]

In the MMRM analysis:

- A [redacted] from baseline was observed for coughing throughout the neoadjuvant period in both arms, with the improvement being clinically

meaningful (defined as ≥ 10-point change) for the placebo chemotherapy arm at Week 12 (mean change from baseline: [redacted] points for perioperative durvalumab plus chemotherapy vs [redacted] points for placebo plus chemotherapy)[33]

- No clinically meaningful changes from baseline were observed for pain in chest and no differences between the treatment arms were observed[33]
- A [redacted] from baseline was observed for dyspnoea in both treatment arms with no differences between the treatment arms[33]

EQ-5D-5L

There was a numerical decrease from baseline both in the EQ-5D index and the VAS scores; without differences between treatment arms (Table 12).[33]

Table 12. EQ-5D-5L index and VAS scores change from baseline over time, with respect to neoadjuvant baseline (mITT)

EQ-5D-5L		Perioperative durvalumab n=366	Perioperative placebo n=374
EQ-5D-5L index score			
Baseline	**n** **Absolute score mean (SD)**	[redacted] 0.8379 (0.15322)	[redacted] 0.8379 (0.15326)
Week 12	**n** **Change from baseline mean (SD)**	[redacted] -0.0369 (0.18529)	[redacted] -0.0244 (0.22071)
Adjuvant baseline*	**n** **Change from baseline mean (SD)**	[redacted] -0.0677 (0.18183)	[redacted] -0.0623 (0.18373)
EQ-5D-5L VAS score			
Baseline	**n** **Absolute score mean (SD)**	[redacted] 75.4 (15.89)	[redacted] 74.2 (17.42)
Week 12	**n** **Change from baseline mean (SD)**	[redacted] -3.7 (19.01)	[redacted] -2.0 (18.15)
Adjuvant baseline*	**n** **Change from baseline mean (SD)**	[redacted] -4.9 (18.29)	[redacted] -5.0 (18.39)

*Adjuvant baseline is the latest measurement after surgery but before the 1st adjuvant dose
Abbreviations: mITT, modified intent-to-treat; SD, standard deviation; VAS, visual analogue scale
Source: AstraZeneca 2023[33]

A 19. The company has carried out a thorough sub-group analysis for EFS and pCR, selecting appropriate variables pre-hoc in the AEGEAN trial. The company is correct to assert that the analyses lack statistical power, which is probably why statistical analyses for differences between strata have not been attempted. In any event, there would be a risk of type II errors (where real differences might remain undetected because of the lack of statistical power) even if a formal statistical analysis had been carried out. Therefore, because detection of sub-group differences is important, there is a need to look for possible effects without the help of statistical testing. For EFS, gender and smoking status appear important effect modifiers. For pCR, programmed cell death ligand-1 (PD L1) expression, lymph node station, disease stage, smoking status and geographic region appear potentially important. If these characteristics do influence the EFS or pCR effects, then any differences in these characteristics between the trial and the target population in England and Wales could affect the representativeness of the EFS effects in the trial and the target population. Please provide the characteristics of the UK target population, including gender, smoking status, PD L1 expression, lymph node station, disease stage and geographic region, so that any possible effects on external validity of trial findings can be evaluated.

Response

The UK target population is aligned with the expected license for perioperative durvalumab: adults with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements. Clinicians at the advisory board held in January 2024 confirmed that the AEGEAN trial was generalisable to the UK patient population.[29] Some minor differences in the percent of males, those with N2 disease and the percent of patients with squamous histology compared to what is seen in clinical practice were noted, but these differences were not seen as a concern to generalisability. For further detail on the generalisability of the AEGEAN trial population to the UK, an advisory board report including a comprehensive summary and analysis of discussions and recommendations made by the UK clinical experts has been provided to the EAG. [29]

Indirect treatment comparison (ITC)

A 20. Priority question. In an anchored matching-adjusted indirect comparison (MAIC), it is important that the common treatment that anchors the analysis (in this case the comparator treatment in each of the two trials) is the same across the two trials. If it is not, then the assumption that (using an outcome expressed as ln odds ratio (OR)) logit (B vs A) - logit (C vs A) = logit (B vs C) [where B and C are the treatments of interest, and A is the common comparator] is no longer tenable. It is not clear that the comparators were the same in this MAIC. The comparator in the AEGEAN trial was neoadjuvant placebo + platinum-doublet chemotherapy (PDC) and adjuvant placebo, whereas in the Checkmate 816 trial the comparator was neoadjuvant PDC, apparently without placebo, and with no placebo given post-op. This constitutes quite a difference, because without placebo the comparator in the checkmate 816 arm may yield less efficacy than otherwise. This will inevitably affect the indirect estimate. It should also be pointed out that in technology appraisal (TA) 876 the Checkmate 816 trial is heavily critiqued as it only includes few European patients. Please estimate the effects these factors may have had on the indirect estimate of the EFS outcome.

Response

Neoadjuvant nivolumab is considered a relevant comparator for this appraisal thus a comparison versus perioperative durvalumab was required. As described in Appendix D, a number of approaches were considered and a MAIC approach was deemed to be most appropriate. Differences in the administration of placebo in the PDC comparator arms are acknowledged as a limitation of the MAIC analysis however, for the purpose of ITCs, placebo + PDC (AEGEAN control arm)[18] and neoadjuvant chemotherapy (CheckMate 816)[7] were treated as common comparators and assumed equivalent. Other factors in addition to control arm characteristics were considered in the feasibility assessment, including differences between trials in patient baseline characteristics. This included region of enrolment, with differences between trials in region (Asia vs non-Asia) accounted for as part of the MAIC.

It is not possible to say categorically what the impact adding placebo to the control arm of the CheckMate 816 trial would have had on the treatment effect. CheckMate 816 was an open-label trial which did not include a placebo in the control arm to match the addition of nivolumab to PDC in the intervention arm.[7] If the hypothesis made by the EAG that the addition of placebo to the control arm of the CheckMate 816 trial might improve efficacy in the CheckMate 816 control arm was true, this would reduce the relative treatment effect of neoadjuvant nivolumab + PDC vs the CheckMate 816 control arm. Accordingly, any bias in the ITC due to placebo would be in favour of nivolumab + PDC.

A 21. Priority question. The covariates in the propensity score weighting used in the anchored MAIC should ideally have covered all the variables that were considered for the perioperative durvalumab vs perioperative placebo sub-group analyses, as all these were assumed to be potential treatment effect modifiers. However, the variables of age, Eastern Cooperative Oncology Group (ECOG) status, race and lymph node station, which were included in the sub-group analyses, were not included in the MAIC propensity score weighting.

a) Please explain why these variables were not selected.

b) If appropriate, please perform another analysis with these variables included.

Response

Race and lymph node station were not reported as baseline characteristics in CheckMate 816[7] and therefore, could not be included as covariates in the propensity score weighting used in the anchored MAIC. In contrast, age (<65 years versus ≥65 years) and ECOG status (0 versus 1) at baseline were available from both studies. Based on the criteria used in the ITC feasibility assessment to select potential effect modifiers (Appendix D.2.1) however, age and ECOG status were not considered to be potential treatment effect modifiers and were not selected as variables for weighting in the MAIC. In addition, Age and ECOG status at baseline were also generally well-balanced between AEGEAN and CheckMate-816 trials (see Appendix D.2.2.2).[7,18]

To explore the impact of including these variables in the MAIC, additional sensitivity analyses have been carried out in which both age (<65 years versus ≥65 years) and ECOG status (0 versus 1) at baseline have been included as factors in the weighting, in addition to those included in the base case and additional scenario. In both cases, the results of these sensitivity analyses were consistent with those presented in Document B.2.9, as shown in the results tables below.

Table 13. MAIC sensitivity analysis EFS HRs for perioperative durvalumab versus neoadjuvant nivolumab + PDC (after weighting in the base case and scenario 1 + inclusion of age and ECOG)

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

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

Age and ECOG status at baseline was included as additional factors in the weighting for the "… + age and ECOG" analyses

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

Table 14. MAIC piecewise EFS HRs (0-to-3-months and 3+ month time intervals) for perioperative durvalumab versus neoadjuvant nivolumab + PDC (after weighting in the base case and scenario 1 + inclusion of age and ECOG)

		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	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Base case + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1 + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Age and ECOG status at baseline was included as additional factors in the weighting for the "… + age and ECOG" analyses

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

Further information from these analyses (baseline characteristics post-weighting; ESS and distribution of weights) are provided below.

Table 15. Baseline characteristics in CheckMate 816 and AEGEAN (unweighted and after weighting to match CheckMate 816 in the base case and scenario 1 + inclusion of age and ECOG)

Characteristic	CheckMate 816 (N=358)		AEGEAN unweighted (N=740)		AEGEAN Base case + age and ECOG (ESS=[redacted])	AEGEAN Scenario 1 + age and ECOG (ESS=[redacted])
	n	%	n	%	%	
Age: <65 years	176	49.2	358	48.4	[redacted]	[redacted]
ECOG status: 0	241	67.3	506	68.4	[redacted]	[redacted]
Planned platinum chemotherapy: cisplatin	258	78.2	196	26.5	[redacted]	[redacted]
Histology: non-squamous	176	49.1	375	50.7	[redacted]	[redacted]
PD-L1 expression: <1%	155	46.5	247	33.4	[redacted]	[redacted]
PD-L1 expression: ≥50%	80	24.0	216	29.2	[redacted]	[redacted]
Region: Asia	177	49.4	305	41.2	[redacted]	[redacted]
Sex: Female	103	28.8	210	28.4	[redacted]	[redacted]
Smoking status: Never	39	10.9	107	14.5	[redacted]	[redacted]
Stage: IIIA	-	57.4	338	45.7	[redacted]	[redacted]
Stage: IIIB	-	12.1	187	25.3	[redacted]	[redacted]

Characteristics with imbalance (≥5% difference) between CheckMate 816 and AEGEAN (red text)

Characteristics included in the weighting to match CheckMate 816 (blue fill)

For CheckMate 816, % PD-L1 expression is calculated using the PD-L1 evaluable population as the denominator (N=333; ~7% not evaluable for PD-L1 expression), and % stage is based on reclassification of patients according to AJCC 8th edition.

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

Age and ECOG status at baseline was included as additional factors in the weighting for each scenario.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; PDC, platinum-doublet chemotherapy; PD-L1, programmed cell death ligand 1

Table 16. ESS of AEGEAN (weighted to match CheckMate 816) in the base case and scenario 1

Arm	Scenario	N	mean weight	median weight	sd weight	min weight	max weight	ESS (%)
Perioperative durvalumab + neoadjuvant PDC	Base case + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative placebo + neoadjuvant PDC	Base case + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative durvalumab + neoadjuvant PDC	Scenario 1 + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perioperative placebo + neoadjuvant PDC	Scenario 1 + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; PDC, platinum-doublet chemotherapy.

Figure 2. Distribution of rescaled weights of AEGEAN (weighted to match CheckMate 816) in the base case and scenario 1

A 22. Priority question. The AEGEAN trial is connected to all relevant comparators, as evidenced by the conduct of anchored ITCs with all comparators. However, the ITCs were separated into one for versus only neoadjuvant nivolumab and a network meta-analysis (NMA) for adjuvant PDC and surgery alone.

a) Why was the estimation of perioperative durvalumab versus neoadjuvant nivolumab not approached through an all-encompassing NMA (that would cover all three decision problem comparators)?

b) **Please conduct an NMA that includes all three comparators.**

c) **For the NMA, given the clinical heterogeneity between trials, please employ the method of multi-level network meta-regression as mentioned by the company in Appendix D and recommended by Phillippo et al. 2020.**

d) **If the combination of all three comparators can be demonstrated to be infeasible then please conduct a Simulated Treatment Comparison (STC) for the comparison with neoadjuvant nivolumab, given the serious concerns about MAICs raised by Phillippo et al.**

Response

As described in Appendix D, a feasibility assessment resulted in a MAIC being chosen as the most appropriate approach for the comparison of perioperative durvalumab versus neoadjuvant nivolumab + PDC.

Since individual patient data (IPD) were available for AEGEAN, both NMA and population-adjusted indirect comparison (PAIC) methods were considered as part of the ITC feasibility based on the methods recommended in NICE DSU TSDs. Multilevel network meta-regression (ML-NMR) is not currently recommended as part of NICE DSU TSD guidance and so was not ultimately explored. As described in Appendix D, a PAIC approach was considered to account for differences between baseline characteristics deemed effect modifiers in AEGEAN and CheckMate 816. No formal guidance exists for selecting between the MAIC and STC as PAIC approaches and evidence in literature review and simulation paper studies is mixed on which approach performs better.[36-38] The theory behind the two approaches was carefully reviewed and a MAIC was considered the method that has less assumptions and is more flexible to perform endpoint analysis by using weighted data. In addition, MAIC approaches have been utilised in a large number of cases in HTA where PAIC have been considered, and so MAIC was also seen as the more established method .[37] Given this rationale, it is not deemed necessary to run an STC for the perioperative durvalumab versus neoadjuvant nivolumab + PDC comparison.

Heterogeneity between studies with adjuvant chemotherapy and surgery were identified however, as described in the submission, in the absence of a clear candidate for pairwise PAIC (and to include evidence from multiple studies), NMA was considered for these comparisons (as per TA876), with sensitivity analyses conducted to explore the impact of heterogeneity between studies. Furthermore, there was insufficient information reported on key baseline characteristics (that were considered potential effect modifiers) from the adjuvant chemotherapy and surgery studies to feasibly conduct PAICs for these comparisons. For example, PD-L1 expression and smoking status at baseline were not reported from these studies, and differences in the staging system versions used between trials makes comparisons of (and adjustments relating to) disease stage very challenging. PAICs were therefore not considered for these comparisons. For the same reason, ML-NMR including comparisons versus adjuvant chemotherapy and surgery (as well as neoadjuvant nivolumab + PDC) would also not be considered feasible. No additional analyses have therefore been conducted.

A 23. Priority question. In the NMA there is clinical heterogeneity across studies and between comparisons in terms of the treatments (i.e., 'neoadjuvant PDC' means different things in different papers), pre-treatments and populations. The sensitivity analyses put forward by the company appear insufficient to account for this. All the sensitivity analysis models have a better fit to the data than the base case, as shown by their much lower Deviance Information Criterion (DIC) values but it is unclear how consistency models and inconsistency models compare to each other in terms of DIC for each scenario.

a) **Please give an overview of clinical heterogeneity in the NMA model - how the studies match in terms of population and treatment.**

b) **Please provide the DIC values for the NMA consistency and inconsistency models for the base case and all the sensitivity analyses.**

Response

Appendix D describes the NMA in detail. Specifically, D.2.1 describes the feasibility assessment for NMA and D.2.3 describes the NMA methodology. Heterogeneity was considered throughout the feasibility assessment and analysis methodology. The DIC values are reported in Appendix D, Table 45.

Consistency should be assessed when there are closed loops of direct evidence on three or more treatments that are informed by at least three independent sources of evidence. In the case of this ITC, the shape of the network does not allow for the fitting of inconsistency models due to the absence of a loop containing both 'direct' and 'indirect' evidence. The only loop contained in the network is the 'direct' evidence from the multi-arm NATCH trial. This applies to both the base case and sensitivity analyses.

A 24. Priority question. The MAIC and the NMA both employed a Cox proportional hazards model, although a piecewise analysis, splitting the analysis into the 0-3 and >3 months epoch, was used to try to avoid the problem of the overall dataset not following the proportional hazards assumption given the probable change in the hazard ratio between the 0-3 and >3 months periods observed in AEGEAN. However, it appears that there was no consideration of non-proportional hazards after 3 months or between durvalumab and any of the comparators outside of the AEGEAN trial i.e. neoadjuvant nivolumab, surgery or adjuvant PDC. Therefore, a method of analysis that relaxes the proportional hazards assumption i.e. using time-dependent hazard ratios would perhaps be more efficient. Please conduct a NMA that employs a method allowing time-varying hazard ratios such as that described by Cope et al. 2020, which was used in NICE TA865.

Response

As described in the CS, the piecewise approach with 3 month cut-point was explored for perioperative durvalumab versus all comparators, based on delayed separation in the AEGEAN trial (perioperative durvalumab versus neoadjuvant PDC). Given the clear rationale for selecting the 3-month time point in AEGEAN (CS Section B.3.3.1)

and the general applicability of this rationale to other neoadjuvant studies (e.g. in CheckMate-816 the first tumour assessment was also planned before surgery [within 14 days]), the piecewise method was deemed a parsimonious way to address the observed pattern and one that would reflect how EFS assessed in the clinical trials is assessed in clinical practice (see response to B.11).

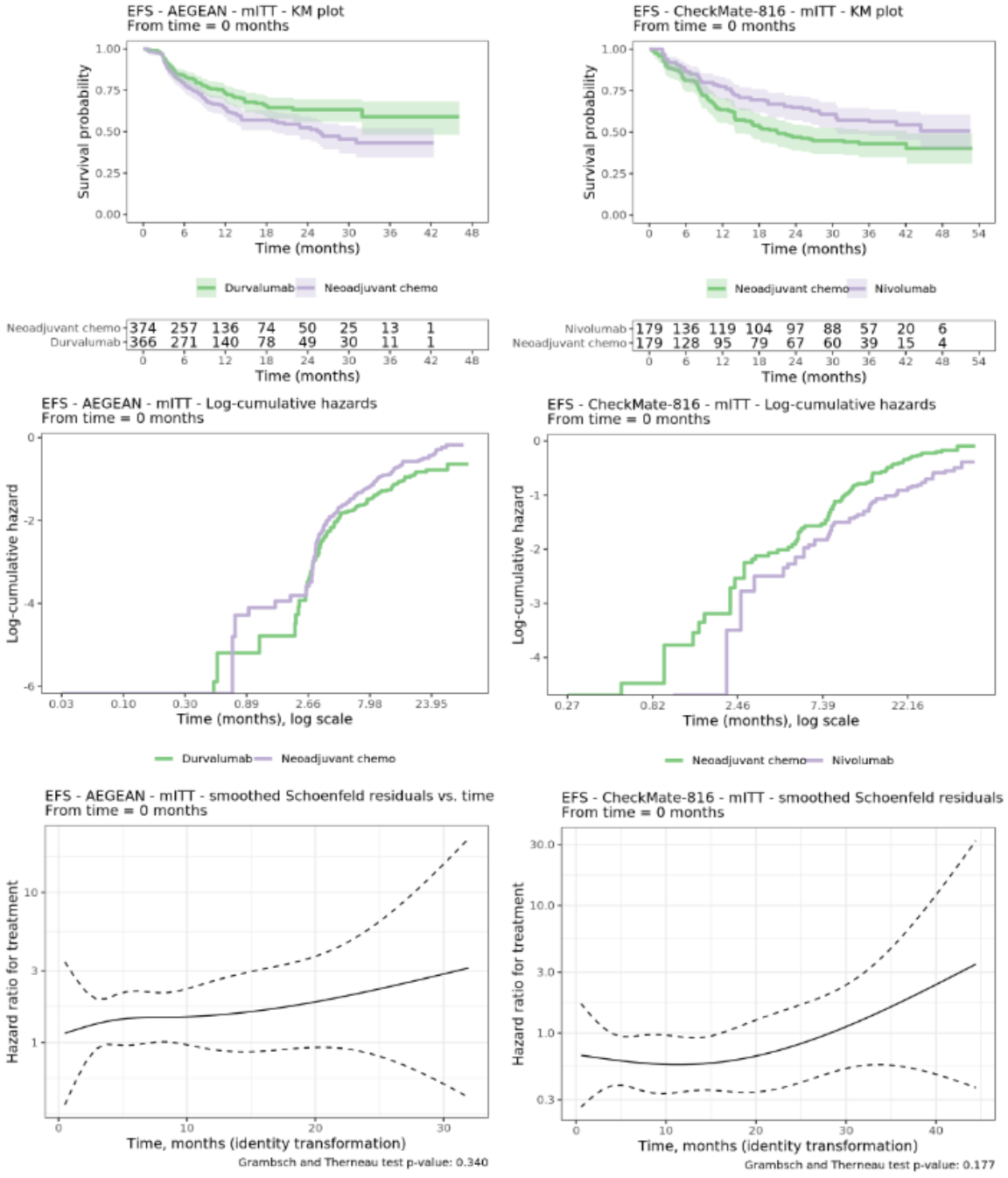
Figure 3 and Figure 4 below show the observed EFS data, log-cumulative hazard plots and smoothed Schoenfeld residuals used to assess proportional hazards for both AEGEAN and CheckMate 816. The improvement in proportionality observed in AEGEAN when assessing only the 3+ months' time interval was not replicated in CheckMate-816. Similarly, evaluations of the proportional hazard assumptions for studies informing comparisons of surgery alone or adjuvant PDC versus neoadjuvant PDC yielded mixed results. In cases where there was separation between arms, a clear or consistent timepoint for this separation was not evident. Nevertheless, across all studies (excluding Rosell 1994 and Li 2012, as per the preferred NMA network),[13,15,39] there is a consistent observation that there is minimal separation between curves during the first 3 months. Hence, a piecewise ITC was explored, utilising a 3+ months cut-point. This approach aligns with the clinical rationale and ensures consistency with the observed data in AEGEAN, and for nivolumab + PDC, the proportional hazards assumption is consistent with the company base case analysis in TA823.[40]

In the cost-effectiveness model, hazard rations (HR)s derived from the piecewise ITC analyses were favoured. This preference was based on the fact that extrapolation was also performed in a piecewise manner. Additionally, this choice aligns with the expectation that none of the model treatments are anticipated to exhibit separation from neoadjuvant PDC within the first 3 months.

A (cost-effectiveness) scenario analysis was conducted to assess the use of the piecewise approach in which the HRs from the ITC (overall period; assuming proportional hazards) was applied. The results were consistent with the 3-month plus piecewise results and demonstrated that model outcomes were minimally affected. This consistency is observed across all comparators.

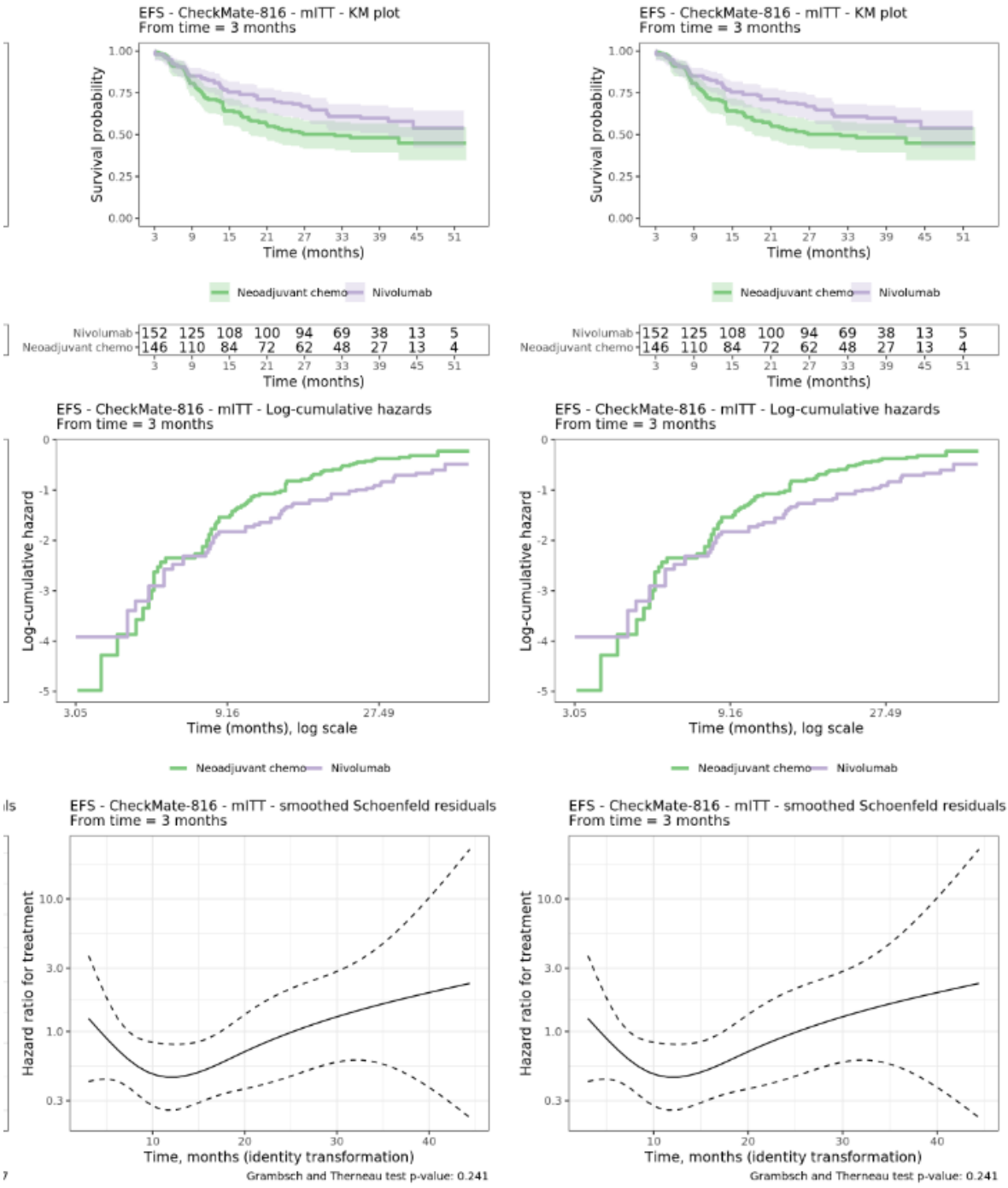
Regarding the request for a parametric NMA, the use of this approach (Cope 2020) requires use of survival distributions fitted to the observed data. However, fitting of survival distributions to the overall trial period in AEGEAN resulted in poorly fitting curves. This discrepancy led to the adoption of piecewise approach for extrapolation in the cost-effectiveness model. In conclusion, a piecewise approach is most appropriate. Further, reference to TA865 is not entirely relevant as it included advanced, unresectable patients being treated to progression with regular RECIST tumour assessments. A similar rationale for piecewise approach would not have been expected in this case.

Figure 3. Proportional hazards assessment for EFS in AEGEAN (mITT population) and CheckMate 816 from time = 0 months (i.e., full follow-up)



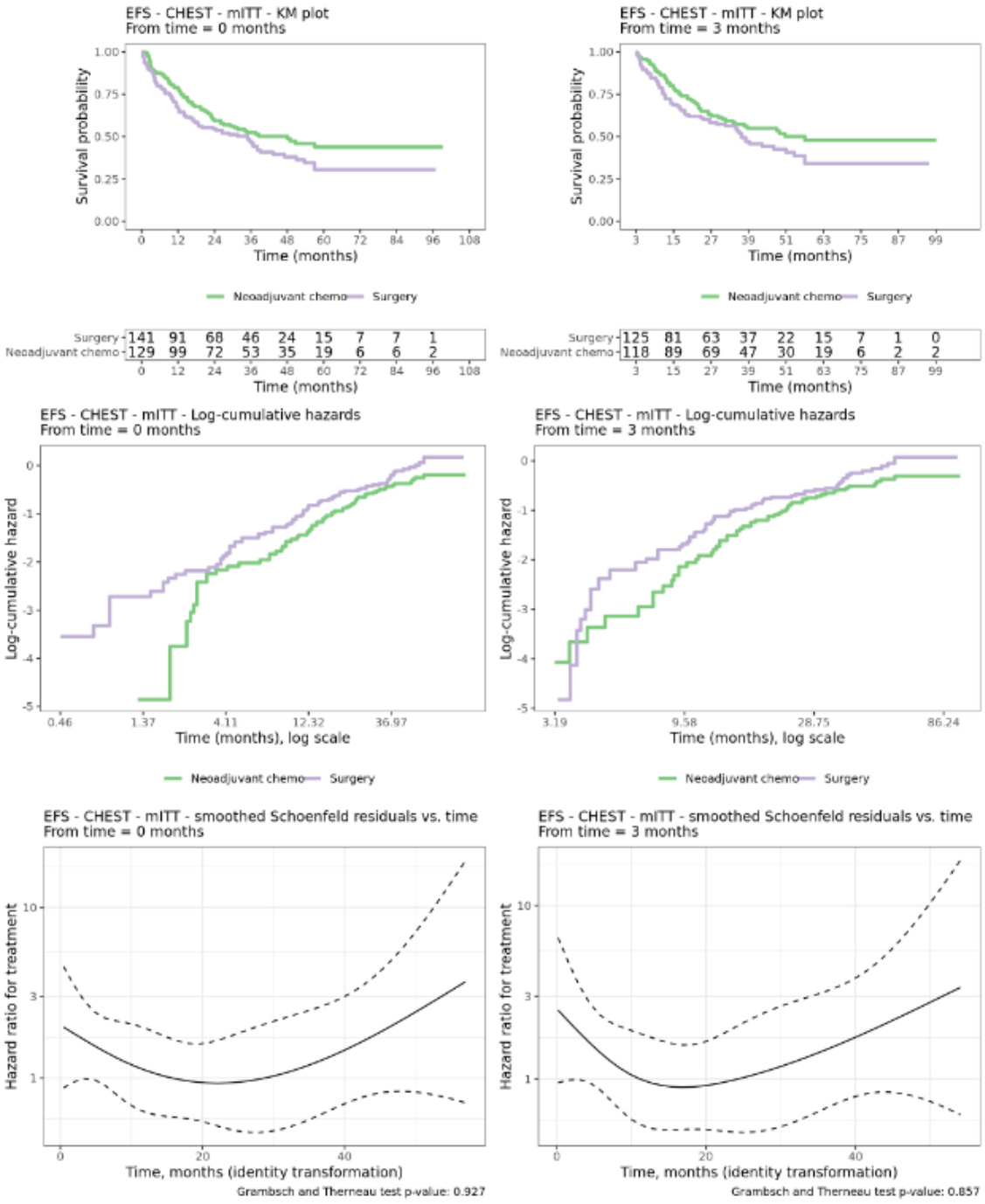
Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

Figure 4. Proportional hazards assessment for EFS in AEGEAN (mITT population) and CheckMate 816 from time = 3 months (i.e., piecewise 3+ month interval)



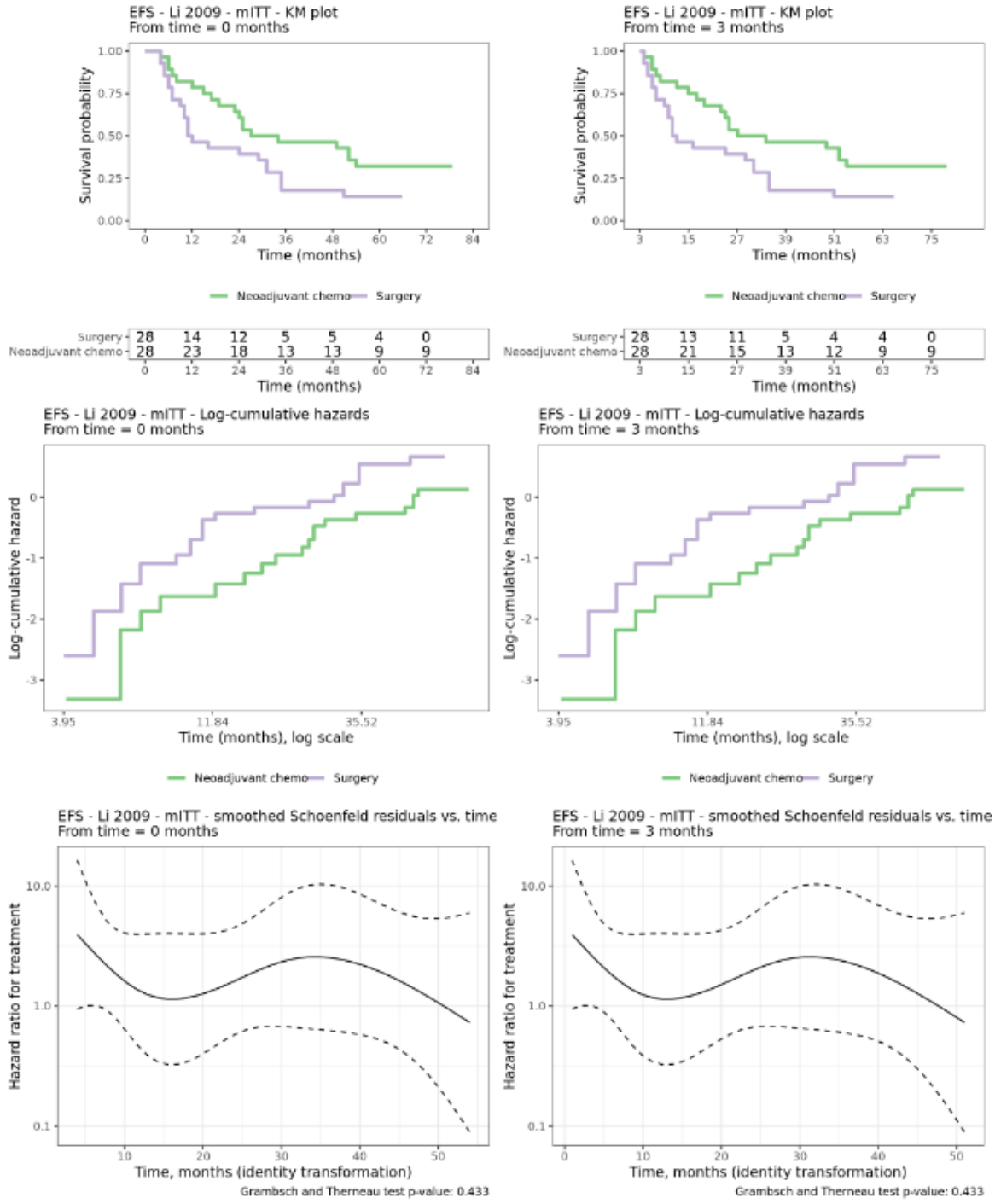
Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

Figure 5. Proportional hazards assessment for EFS in CHEST (mITT population) from time = 0 months and from time = 3 months



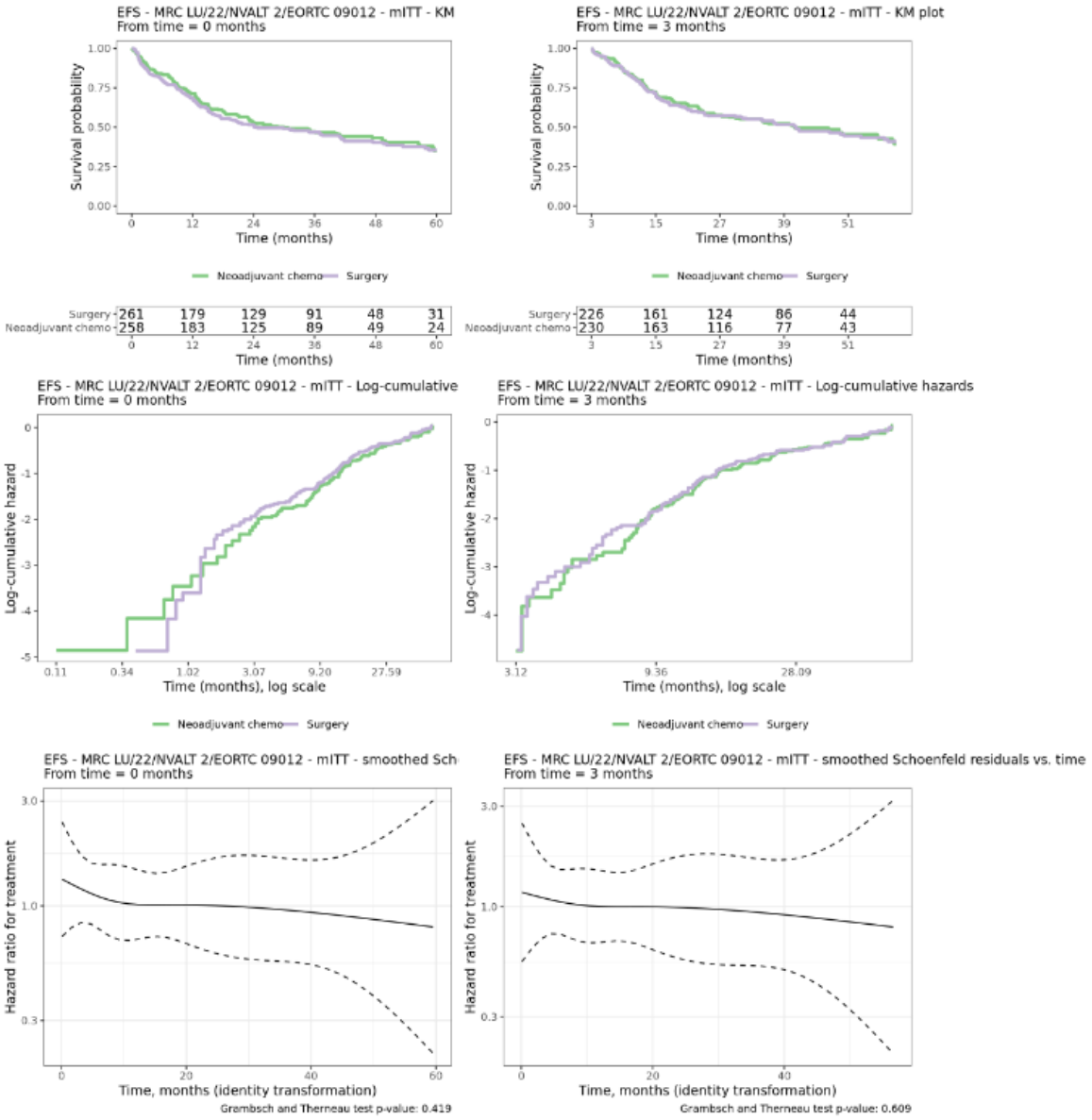
Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

Figure 6. Proportional hazards assessment for EFS in Li 2009 (mITT population) from time = 0 months and from time = 3 months



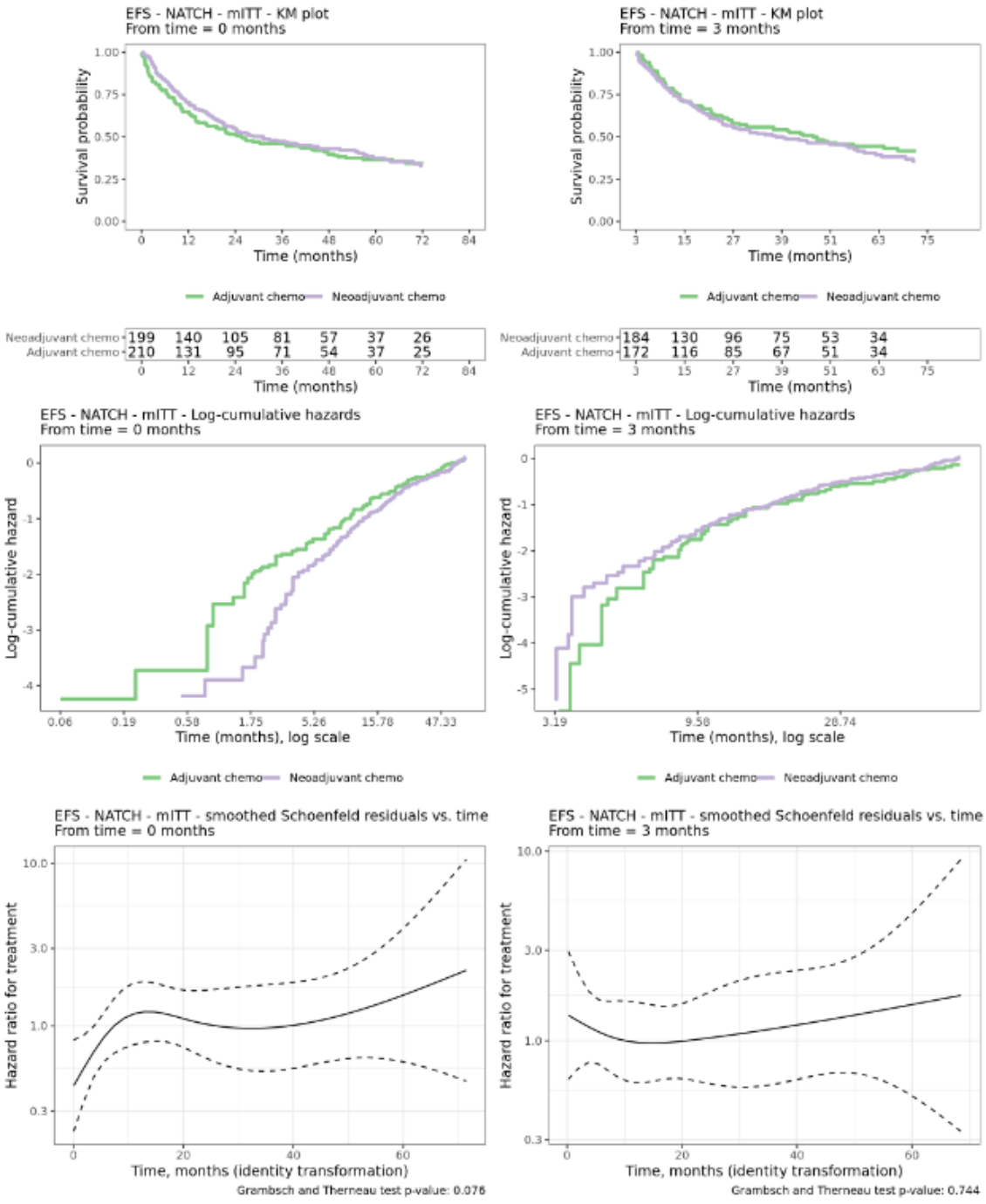
Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

Figure 7. Proportional hazards assessment for EFS in MRC LU/22/NVALT 2/EORTC 09012 (mITT population) from time = 0 months and from time = 3 months



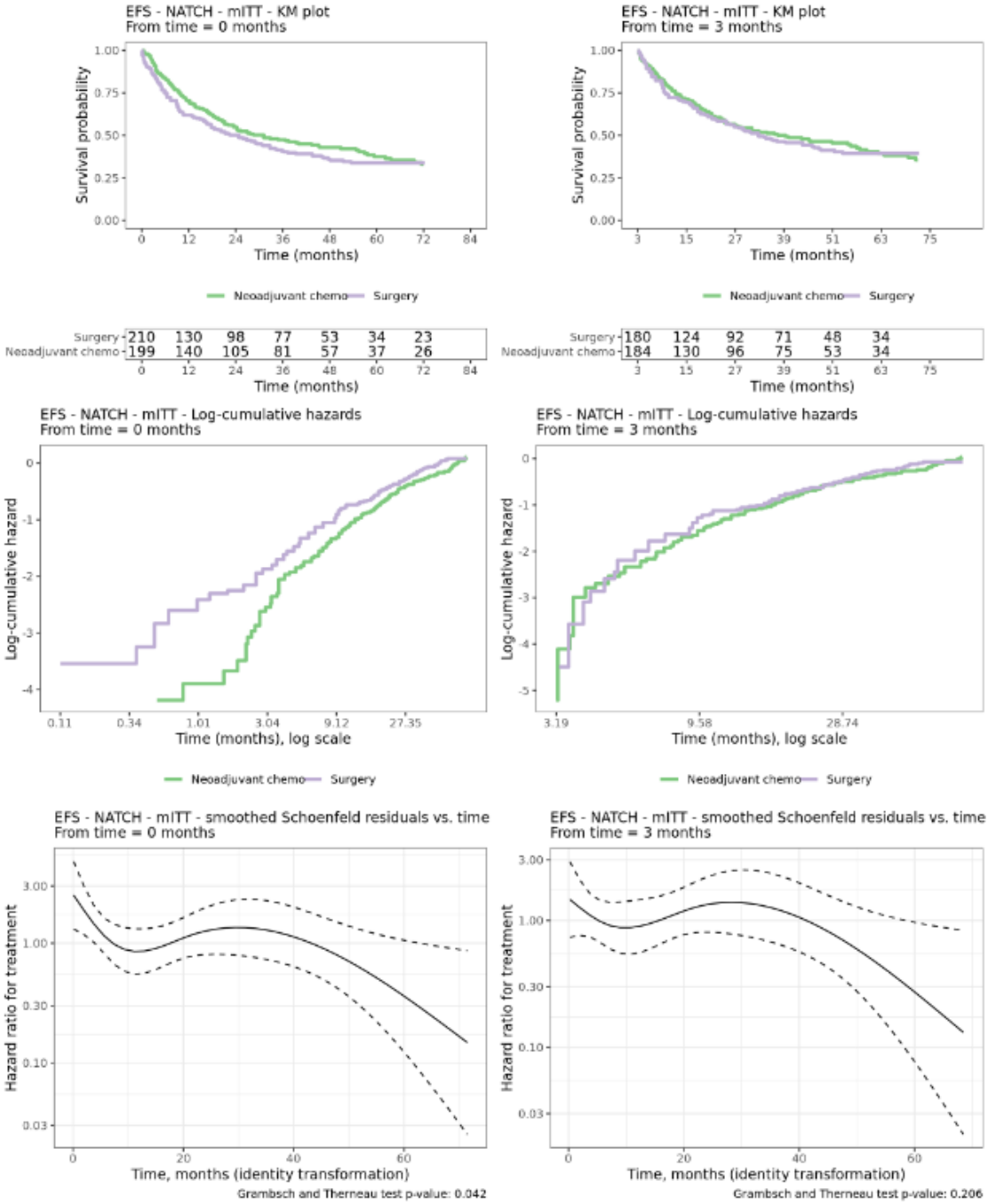
Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

Figure 8. Proportional hazards assessment for EFS in NATCH (adjuvant PDC) (mITT population) from time = 0 months and from time = 3 months



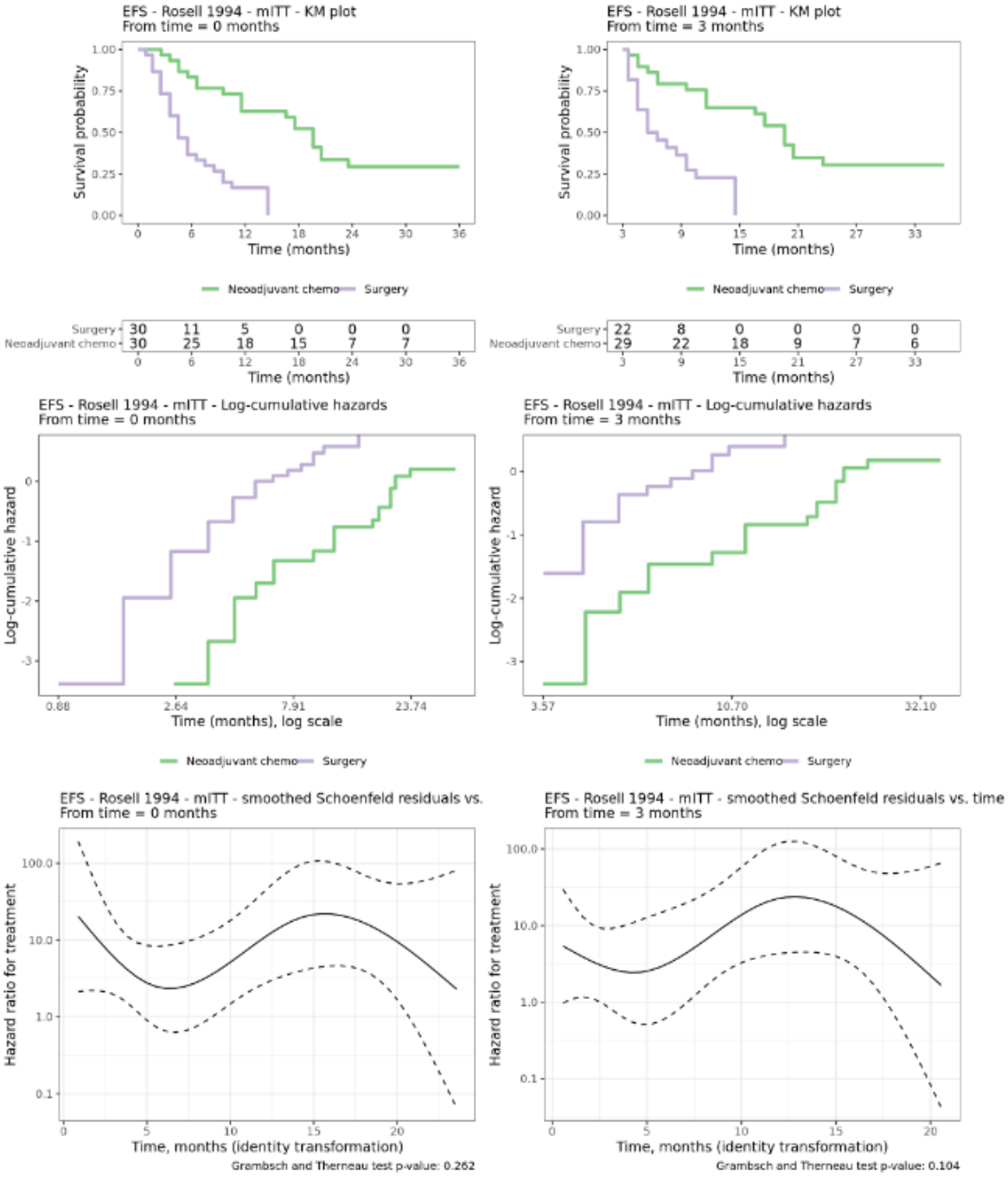
Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat; PDC, platinum-doublet chemotherapy

Figure 9. Proportional hazards assessment for EFS in NATCH (surgery) (mITT population) from time = 0 months and from time = 3 months



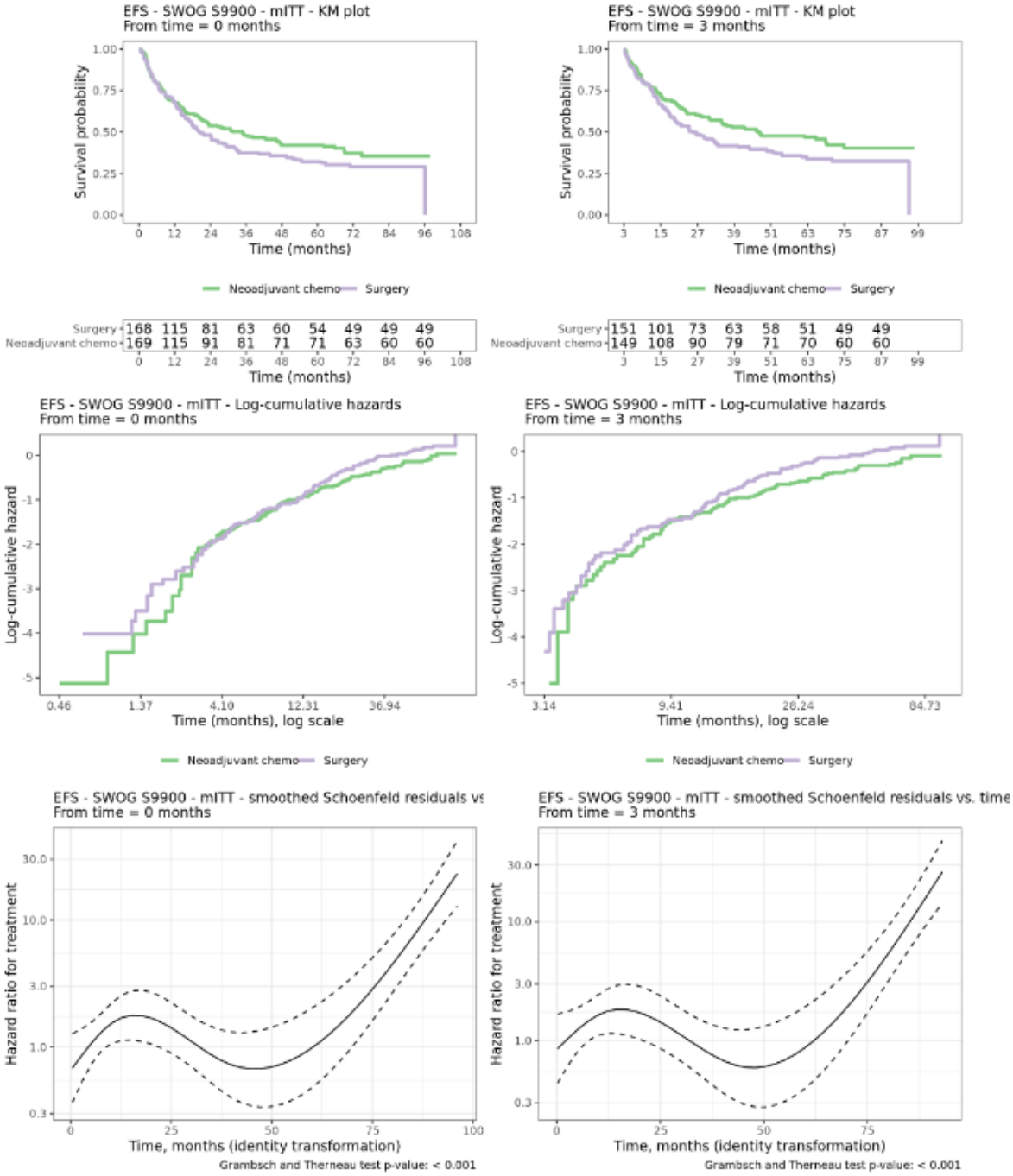
Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

Figure 10. Proportional hazards assessment for EFS in Rosell 1994 (mITT population) from time = 0 months and from time = 3 months



Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

Figure 11. Proportional hazards assessment for EFS in SWOG S9900 (mITT population) from time = 0 months and from time = 3 months



Abbreviations: EFS, event-free survival; KM, Kaplan-Meier; mITT, modified intention to treat

A 25. The only outcome to be subjected to ITC (MAIC or NMA) was EFS. Please explain why other outcomes were not subject to ITC.

Response

Event-free survival was considered the most relevant outcome for the ITCs as it assesses the full perioperative approach as defined by the NICE final scope, considers the occurrence of multiple patient-relevant events, provides a direct measure of treatment efficacy across both neoadjuvant and adjuvant treatment periods with surgery as a curative intent therapeutic strategy, and is not confounded by subsequent therapy following progression or recurrence.

Surgery with neoadjuvant and/or adjuvant therapy is given with curative intent, with the aim to completely remove the primary tumour and reduce the risk of any subsequent recurrence. Progression precluding surgery or recurrence after surgery are both highly relevant events for patients, given the impact of progression/recurrence on subsequent prognosis and HRQoL.[41-44]

In AEGEAN, EFS is defined as the time from randomisation to an event of disease progression that precludes surgery, local or distant recurrence, or death due to any cause.[18] Since EFS includes progression events precluding surgery, recurrence events after surgery, and death, it is aligned with the treatment goals of this setting and measures the success/failure of neoadjuvant followed by adjuvant therapy.

In addition to the intrinsic value of EFS as an endpoint in this setting, EFS is also a surrogate for OS.[45-47] Overall survival is evaluated in AEGEAN; however, a longer trial follow-up is needed as at the time of EFS IA1, OS data had 22% maturity and per the MTP, OS was not formally assessed. Thus, for early-stage NSCLC therapies such as perioperative durvalumab, the outcome of EFS, which considers multiple patient-relevant events (disease progression precluding surgery, disease recurrence after surgery, and death) and is also a surrogate outcome for OS, has more value in this setting.[45]

The second primary outcome of AEGEAN was pCR but this was not considered an outcome of interest for ITC. Pathological complete response is an early indication of treatment efficacy and a stringent indication of response to treatment in the neoadjuvant setting.[48] Due to the early nature of the resectable NSCLC and its improved prognosis versus metastatic disease, pCR is an endpoint that is highly relevant to patients with resectable NSCLC receiving neoadjuvant therapy. However, the potential impact of adjuvant therapy on long-term outcomes (EFS and OS) is not

captured by pCR. As such, EFS is considered a more relevant outcome to evaluate the full perioperative approach of durvalumab by ITC to inform the cost-effectiveness model.

Quantitative synthesis of safety data was not conducted as it was considered inappropriate given the differences in treatment regimens and the sparseness of the data across the studies. Adverse events of the different treatment regimens have been taken into account in the cost effectiveness model, informed by safety data from the AEGEAN trial (Grade 3-4 AEs with incidence ≥ 5% in any treatment arm) for AEGEAN therapies and literature (for non-AEGEAN therapies).

Section B: Clarification on cost-effectiveness data

Literature searches

B 1. A de novo systematic literature review (SLR) was conducted to identify resource use and costs, and HRQoL evidence in resectable Stage I-III NSCLC.

a. Please justify why stage IV disease was not included in the SLR to identify resource use and costs and HRQoL evidence for patients with distant metastases.

b. Please update the SLR by including stage IV disease and elaborate on the appropriateness of the additionally identified studies for informing resource use and costs and utility values for the distant metastasis (DM) 1 and DM2 health states in the economic model.

Response

The SLR was conducted for the population of interest for the NICE appraisal and the expected marketing authorisation for perioperative durvalumab. This is resectable NSCLC (Stage I-III). Studies identified as relevant by the Stage I-III search captured resource use and costs reflective of the starting population in the economic model. A number of identified studies covering resectable lung cancer included DM health states that captured resource use, costs and HRQoL in this context and therefore

covered DM in an appropriate manner. This approach assures patients that begin as resectable are not excluded and considers cost and resource use once they recur. This approach is consistent with the search approaches in both TA876 and TA823.[30,49,50]

Population

B 2. The final NICE scope states that subgroups should be considered (if the evidence allows) based on 1) whether durvalumab is used before and after surgery, and 2) PD-L1 tumour proportion score. The company stated that "*Whilst pre-specified subgroup data from AEGEAN are presented in this submission, including for PD-L1 expression and disease stage (Section B.2.7), the cost-effectiveness analysis is based on the full mITT"* (modified intention-to-treat). Please provide these subgroup analyses, as well as an updated model file including these analyses

Response

Given the perioperative nature of the treatment being appraised (durvalumab with PDC as neoadjuvant treatment followed by durvalumab monotherapy as adjuvant treatment), conducting subgroup analyses based on treatments before or after is not appropriate or relevant in a cost-effectiveness analysis.

Regarding the prespecified subgroup analysis for PD-L1 expression, an EFS benefit was observed and there was a consistent treatment effect across the mITT population and PD-L1 subgroup. In addition, the expected regulatory license will not include a restriction based on PD-L1 status therefore, the focus remains on the overall mITT population for the cost-effectiveness analysis.

Intervention and comparators

B 3. Priority question. As described in clarification question A7 above, neoadjuvant chemoradiotherapy was excluded as a comparator from the decision problem based on clinical opinion. Please provide scenario analyses, as well as an updated model file including neoadjuvant chemoradiotherapy as a comparator.

Response

It is not appropriate to provide a scenario analysis including neoadjuvant CRT as a comparator.

As stated in the response for A7, although neoadjuvant CRT is recommended in NG122[26] for stage IIIA-N2 patients, this is a small subset of patients equating to roughly 7% of NSCLC patients, which are not typically considered resectable. Duan et al, 2020[27] demonstrates that the population of patients eligible for neoadjuvant CRT is only about 7% of NSCLC patients and Adizie et al, 2019[28] reported CRT being administered in only 5% of stage IIIA NSCLC patients in England. Clinicians in attendance at the 2024 UK advisory board[29] unanimously agreed that neoadjuvant CRT is not offered to patients with resectable NSCLC in UK clinical practice. This is further supported by clinical expert opinion gathered for TA876[30], where neoadjuvant CRT was described as typically being reserved for patients considered to be unresectable. As such, neoadjuvant CRT is not a comparator of interest for this appraisal and is therefore appropriately excluded from comparative clinical and cost-effectiveness analyses.

Model structure

B 4. Priority question. The CS stated that an "assumption was made that those patients who received BSC in LRR" … "would transition to the death state directly (i.e., not transition to DM and receive further treatment)". In other words, patients receiving best supportive care (BSC) in the locoregional recurrence (LRR) health state are assumed to die in a month after experiencing a LRR and cannot transit to the distant metastasis (DM) health state.

a) Please provide supporting evidence to justify this assumption.

Response

This assumption is in line with that used in TA823,[40] whereby patients receiving BSC in LRR were assumed to transition directly to death given that they would not receive further treatment. In line with TA823, the efficacy inputs were sourced from Wong et

al. 2016 utilising overall survival data for BSC.[43] This assumption was deemed appropriate when the model structure was presented to UK clinical experts in an advisory board.[29]

b) Please provide an overview of the total proportion of patients that receive BSC in the LRR health state (over the model time horizon), conditional on the CS base-case, per treatment considered.

Response

The proportion of patients receiving BSC in the LRR health state is 20.5% (informed by Wong et al. 2016)[43] and is assumed to be the same across all treatment arms. The total proportion of patients is 8.2% after accounting for the proportion of patients transitioning from the EF to the LRR health state ([redacted]) across all treatment arms.

c) Please provide scenario analyses, as well as an updated model file including these analyses, relaxing this assumption by:

i. Assuming no patients would receive BSC in the LRR health state (i.e. all patients are proportionally distributed over the active treatments provided in the LRR health state)

ii. Assuming patients that receive BSC in the LRR health state have equal transition probabilities as used for CRT (also allowing the transition to DM)

iii. Assuming patients that receive BSC in the LRR health state have equal transition probabilities as used for RT (also allowing the transition to DM)

Response

The assumptions used in the base case were deemed appropriate based on previous evidence used in TA823,[40] and validated by clinical experts at a UK advisory board.[29] As such, relaxing these assumptions were not deemed appropriate given the lack of relevant evidence to support these proposed scenarios.

B 5. The CS states that 18% of patients having no retreatment would have single modality radiotherapy (RT) in the locoregional recurrence health state in line with TA761. However, Table 42 of the CS states that 82% of people have RT and 18% have chemoradiotherapy. It appears this error has been carried forward into the model ("Efficacy" tab, Cells F and I 174:175). Please correct this in the model, submission and any updated cost-effectiveness estimates.

Response

The error has been fixed in the cost-effectiveness model. In addition ("Tx Shares & Costs" tab, Cell F156 which is linked to the "Efficacy" tab, Cells F, G, H, I 173:175 in the model), the previous values have been replaced by the same "p_" values, i.e., the values that are sent through the "Parameters" tab, to enable uncertainty to be accounted for. The impact of this discrepancy on the model outcomes is small. The updated weights are presented in Table 17.

Table 17. Survival curve weights based on treatments received in LRR

EF treatments (columns) LRR treatments (rows)	Perioperative durvalumab		Neoadjuvant PDC	Reference to section in submission
	No IO retreatment	IO retreatment		
CRT followed by durvalumab	0.0%	46.6%	46.6%	Section B.3.5.3.1
RT	18.0%	9.6%	9.6%	Section B.3.5.3.1
CRT	82.0%	43.8%	43.8%	Section B.3.5.3.1

Abbreviations: BSC, best supportive care; CRT, chemoradiotherapy; IO, immuno-oncology; LRR, locoregional recurrence; PBO, placebo; RT, radiotherapy.

B 6. Priority question. The company adopted a state transition modelling approach, rather than the partitioned survival model that is commonly used in oncology. State transition modelling allows using external sources of evidence and thus is not reliant on extrapolation of immature OS data. As stated in the CS, the use of state transition models may be deemed appropriate in cases where the cost

effectiveness analysis requires a complex disease pathway to be analysed.

a) **Please justify that the current disease is considered a complex disease pathway that requires the use of a state transition model.**

Response

Non-small cell lung cancer encompasses a diverse group of lung cancers, each with distinct histological and molecular characteristics. This heterogeneity leads to variations in disease progression, treatment responses, and overall outcomes. A state transition model allows for the incorporation of these diverse pathways, providing a more accurate representation of the disease. Additionally, treatment typically involves various lines of therapy, including surgery, chemotherapy, immunotherapies, and combinations. State transition models can capture the nature of these treatments and the transitions between different health states based on patient responses and disease progression. Finally, modelling resectable NSCLC requires long-term follow-up due to the potential for late-stage recurrences. State transition models allow for the simulation of extended time horizons, enabling the assessment of the long-term cost-effectiveness of different treatment plans.

b) **Please provide an overview of similarities and differences with TA876 in terms of model structure and related assumptions.**

Response

Similarities:

Both models include 4 health states: Event-Free (EF), Locoregional Recurrence (LRR), Distant Metastasis (DM), and Dead. All patients enter the model in the EF health state, where patients may experience 1 of 2 types of progression: LRR or DM. Additionally, patients in the EF health state may also die, moving to the Dead health state. Patients in the LR health state may experience further progression, moving to the DM or Dead health states. Patients who develop metastases and move to the DM state from either EF or LRR, can only move to the death state from this point onwards.

Differences:

As detailed in the CS, when patients experience DM, the probability of transitioning to death relies on the use of a nested PSM. This approach captures the impact of progression within the DM state in terms of costs and HRQoL, as well as the effect of treatments received within the DM state in terms of LYs and QALYs. PFS and OS data from the pivotal clinical trials of SoC were used to partition time to death into two tunnel states: progression-free within DM (DM1) and progressed disease within DM (DM2). The PFS and OS data were extrapolated, and weighted average PFS and OS curves were obtained based on the treatment market shares assigned in the DM state. DM1 was informed by PFS, whilst DM2 was informed by the difference between OS and PFS (i.e., post-progression survival or PPS). This approach distinguished costs and QALYs accrued pre- and post-progression.

In TA876, when patients experience DM, a one-off cost, QALY, and life-year (LY) total representing subsequent treatment mix is applied; further outcomes are no longer explicitly tracked, and the patient does not make any further state transitions. Patients in all health states except DM are subject to a probability of death each cycle (for patients in DM, this probability is only considered in the LY and QALY total applied).

c) **In the current application, state transition models allow more flexibility to estimate costs and consequences post progression. Particularly given that the EFS hazard ratios (HRs), that relate to event-free (starting) health state, are the most influential input parameters. Please justify that in this specific case, the additional complexity of a state transition model is required to estimate long term costs and consequences.**

Response

The state transition model is crucial for capturing the complexities of treatments received by NSCLC patients, particularly those entering the LRR and DM health states. Different treatments, such as IO, chemotherapy, or radiotherapy, are administered based on their treatment history. This model comprehensively includes the LRR and DM health states, enabling the assessment of long-term costs and

outcomes associated with patients progressing at different times and subsequently undergoing different treatments in later stages. Notably, individuals progressing into the LRR health state are expected to have a longer life expectancy and higher quality of life than those progressing into the DM health state.

d) **To estimate the long-term costs and consequences, time-dependent transition probabilities (TP4-6 in CS Figure 20) are estimated for the LRR and DM health states. These parametric survival models are estimated based on external sources of evidence, with transition probabilities as a function of the model cycle time. However, patients enter the LRR and DM health states at different points in time. Hence, the transition probabilities should be implemented as a function of the time since entry into the LRR or DM health state (rather than as a function of the model cycle time). This discrepancy might bias the estimated cost and consequences. Please justify the current approach given the above and elaborate on the potential bias this might induce.**

Response

External sources of evidence provide data on survival and transition probabilities based on the model cycle time, which is common practice in survival analysis. This approach is the most robust, given the absence of additional data. Without access to patient-level data from these trials, implementing transition probabilities as a function of the model cycle time was undertaken to maintain simplicity and transparency within the model.

e) **There are multiple potential solutions to overcome the discrepancy described above regarding transition probabilities as a function of the model cycle time versus transition probabilities as a function of the time since entry into the LRR or DM health state. This includes the use of transition probabilities that are constant over time, the inclusion of tunnel states and the use of patient-level simulation. Please elaborate on the implications of this discrepancy and report on the potential impact on the estimated costs and consequences using scenario analysis.**

Response

The current approach was performed to reduce model complexity and increase transparency of the calculations. Selecting an exponential distribution can be used in the model for each health state, which would use constant transition probabilities – however, the poor fit to the data does not merit such an approach and is therefore difficult to justify. The lack of available data to model tunnel states, as well as the lack of precedent for utilising patient-level simulation based on prior NSCLC submissions did not merit the use of these approaches.

f) Please adopt a partitioned survival model approach to validate the current state-transition model approach and report the results.

Response

It is not appropriate to adopt a partitioned survival model (PSM) approach for the following reasons:

- A PSM involves dividing the disease pathway into distinct phases and modelling each phase separately. NSCLC progression is characterised by multiple stages and transitions between health states (e.g., LRR and DM). Therefore, a PSM may oversimplify the progression dynamics, potentially leading to an incomplete representation of the disease pathway.
- The PSM will struggle to adequately capture the sequencing of different treatments over time, particularly in cases where patients receive various therapies in response to disease progression. Given the diverse treatments involved in NSCLC, the ability to represent treatment sequences and their impact on costs and outcomes is key.
- NSCLC treatment responses can vary, and patients transition between different health states based on their responses and disease progression. A PSM is unable to model these dynamic changes, therefore would overlook nuances in the long-term costs and outcomes associated with different treatment strategies.

- The interactions between health states (LRR and DM) are complex. The state transition model captures these interactions by allowing for the simulation of patients moving between states based on their treatment responses. A PSM is unable to adequately represent these complex dynamics.

B 7. Priority question. The CS stated that "*the model assumes that 95% of patients would achieve cure if they have not experienced an EFS event at 5 years*". In the CS this assumption was stated to be consistent with TA569 (early-stage breast cancer) and TA642 (relapsed or refractory acute myeloid leukaemia). Moreover, the cure assumption might be debatable as in the TA876 final appraisal document (FAD) it was stated that *"The EAG considered that there was no convincing clinical evidence to support how the cure assumption had been modelled. It was noted that there is generally a consensus among clinical experts that cure occurs between years 5 and 8. But there is no consensus on the rates of cure, and the empirical evidence to support this assumption is lacking."*

a) Please justify that the cure assumption from TA569 and TA642, which consider different disease areas, is appropriate. Also considering the TA876 FAD comments highlighted above.

Response

During a UK advisory board in January 2024, clinicians specialising in NSCLC unanimously endorsed the plausibility of cure, deemed the 5-year timeframe appropriate, and agreed that a proportion of 90-95% of patients achieving cure was reasonable.[29] In addition, previous NICE appraisals in NSCLC (TA761 and TA876) have established an assumption that 95% of patients would achieve cure.[30,49] This aligns with the proportion of patients in Sonoda et al. 2019 (as employed in TA823), who experience recurrence beyond 5 years, without experiencing it within the initial 5 years post-surgery.[40,51] As such this merited sufficient justification for its use in the model base case.

b) **Please provide an overview of the total proportion of patients that are assumed cured, conditional on the CS base-case, per treatment considered.**

Response

An overview of the total proportion of patients that are assumed to be cured (conditional on the CS base-case) across all treatments is presented below (Table 18). The total proportion of patients assumed to be cured was calculated as the product of [patients assumed to be cured, i.e., 95%] * [patients remaining at EF health state at the cure timepoint, i.e., 5 years].

Table 18. Proportion of patients assumed to be cured

Comparator arm	Perioperative durvalumab	Neoadjuvant PDC	Neoadjuvant nivolumab + PDC	Adjuvant PDC	Surgery alone
Total proportion of cured patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PDC, platinum-doublet chemotherapy

c) **Please provide supporting evidence to validate the proportions of cured patients, per treatment considered.**

Response

As previously mentioned, and considering input from clinical experts, NICE appraisals in NSCLC (TA761 and TA876), and published evidence (Sonoda et al. 2019) [29,30,49,51], the assumption of a 5-year cure rate for 95% of patients remaining event-free was considered clinically plausible. While these proportions weren't directly validated across all treatment arms, their plausibility stems from the confidence in the validated cure assumption.

d) **Please clarify what the "warm-up" period entails, as specified in CS Table 94 and provide a detailed description how this was adopted in TA876 (which is referred to in CS Table 94)**

Response

In line with TA761 and TA876,[30,49] in the CS the "warm-up" period entails an interim period whereby the percentage of patients assumed to be cured is gradually increased at a proportional rate, i.e., demonstrating a more continuous flow in the percentage of patients cured, rather than an immediate application of the cure assumption.

A scenario analysis was conducted whereby cure at 5 years was assumed with a warm-up period of 1 year. This scenario was included to test the impact of a different cure assumption, more in line with the cure assumption that was applied in TA876.[30] However, we found a small error in how this scenario was incorporated in the model as the TA876 base-case comprised of cure at 5 years with 2 years warm-up period (instead of 1 year warm-up). We have therefore updated this in the scenario analysis and economic model.

e) **Please justify the assumption that the cure assumption involves maintaining an event-free status for patients until death.**

Response

In the treatment of NSCLC, the aim is to achieve remission, whereby the cancer is no longer detectable and does not return. In line with this goal, the definition of cure within the model is aligned with this objective.

f) **Please justify why the current cure assumption was adopted rather than (non-)mixture cure models (e.g. as described in NICE DSU TSD 21).**

Response

(Non-)Mixture cure models are appropriate to use when there are sufficient data available to reliably estimate a cure fraction. Sufficient numbers at risk in the tail of the distribution are needed to reliably estimate this cure fraction.

g) **Please provide scenario analyses, as well as an updated model file including these analyses, exploring the cure assumption by:**

   i. **Assuming no cure**

ii. **Assuming 50% is cured at 5 year**

iii. **Assuming 10% is cured at 5 year**

iv. **Assuming 95% is cured at 8 year**

v. **Assuming 50% is cured at 8 year**

vi. **Assuming 10% is cured at 8 year**

vii. **Assuming 95% is cured at 10 year**

viii. **Assuming 50% is cured at 10 year**

ix. **Assuming 10% is cured at 10 year**

Response

The base case utilised in the model (95% cured at 5 years) was deemed appropriate based on clinical expert opinion as well as precedent made in previous NSCLC submissions to NICE. The list of scenarios requested here are not based on clinical evidence within NSCLC and, as such, were not included in the model file. Instead, an alternative scenario was investigated, incorporating a warm-up period of 24 months starting from year 5, in accordance with NICE TA876.[30]

B 8. The company submission states that IO retreatment is not permitted in the model for those whose disease progressed within 6 months of completing an immunotherapy regimen in the EF state.

a) Please confirm whether this same restriction is applied to people who progressed within 6 months of having cCRT and durvalumab in the LRR health state. (I.e, are these people prevented from having an immunotherapy containing regimen in the DM health state?)

Response

Within the model, patients can undergo IO retreatment in the DM health state if they have already received IO treatment in the LRR health state. This is assumed to be captured within the input that specifies the proportion of patients receiving IO in DM.

This is 80% in the base-case of the CS, based on TA683 and TA770 resource impact templates.[52,53]

The modelling decision stems from a preference to limit model complexity, as applying the 6-month IO treatment restriction for patients progressing from LRR to DM would require tracking patients from entry to LRR until a specified time-period, incorporating additional matrices and making assumptions like those used in EF. For instance, assuming IO retreatment only if no progression occurs within 6 months of completing IO in LRR. TA798 did not explicitly model IO retreatment, therefore there is no precedence for this approach in this setting.[30]

A scenario analysis to test the impact of using a lower percentage of patients receiving IO in DM has been added to the economic model (see Question B.8.b). This scenario resulted in a minor impact on the outcomes when comparing perioperative durvalumab against neoadjuvant nivolumab, yet a larger impact was seen when comparing perioperative durvalumab versus non-IO comparators (see Clarification Appendix). The allowance for IO retreatment is confined to LRR or DM states only after initial IO treatment in the EF health state.

b) If this restriction is not currently modelled, please update the model to include it or provide justification for omitting it from the model?

Response

As discussed above, the IO restriction from LRR to DM health state is not modelled because this would lead to an overcomplicated treatment pathway. To test the impact of this limitation, a scenario analysis has been added to the economic model and CS, whereby the percentage of patients receiving IO in DM health state (where applicable, based on IO rules), is reduced from 80.0% (base-case) to 65.3%. This scenario had a minor impact (i.e., 6.7%) on the ICER of perioperative durvalumab against neoadjuvant nivolumab. The impact on the ICERs of perioperative durvalumab against non-IO comparators (i.e., neoadjuvant PDC, surgery alone and adjuvant PDC) was larger, but all ICERs remained below £10,000/QALY.

This percentage was derived using the following calculations:

Based on model predictions, on average, [redacted] of patients transition from the LRR health state to the DM health state (as observed in the neoadjuvant PDC arm). Within this group, 37.1% are assumed to have undergone IO treatment in LRR, either in the absence of IO in the EF health state or if IO retreatment is allowed.

Additionally, the proportion of patients assumed not to have progressed within 6 months of completing chemoradiotherapy (CRT) followed by durvalumab, as calculated in the economic model (i.e., LRR health state modelling) (12 months CRT followed by durvalumab and 6 months waiting for IO retreatment, i.e., 18 months PFS in the CRT + durvalumab arm of PACIFIC), is calculated at [redacted].

Thus, the percentage of patient's ineligible for IO in DM1 due to IO retreatment in LRR, is calculated as follows: [redacted] * 37.1% * (100.0% - [redacted]) = 14.7%. Based on the resource impact templates from TA683 and TA770, where 80% is assumed to receive IO retreatment in DM1, the scenario calculates the total number of patients receiving IO in DM after IO in LRR as 80.0% - 14.7% = 65.3%.

Effectiveness

B 9. Priority question. The HRs used in the economic model are reported in CS Table 35 (perioperative durvalumab versus neoadjuvant PDC HR = [redacted]), CS Table 38 (neoadjuvant PDC + nivolumab versus neoadjuvant PDC HR = [redacted]) and CS Table 39 (surgery alone versus neoadjuvant PDC HR = [redacted] and adjuvant PDC versus neoadjuvant PDC HR = [redacted]). These HRs seem however inconsistent with the clinical effectiveness section of the CS (though reference is made to CS section 2.9). The EAG believes it is crucial to be transparent about the methods used to derive the HRs and the HRs used in the economic model to be consistent with the clinical effectiveness section.

a) **The EAG could not find the abovementioned HRs in the clinical effectiveness section. Please provide:**

   i. **detailed references where the abovementioned HRs can be found / derived from the clinical effectiveness section of the CS.**

ii. **the methods used to calculate the abovementioned HRs.**

b) **Please provide detailed justification for not using the 'base case' HR's as specified in the clinical effectiveness section of the CS, i.e. those reported in CS Table 20, CS Table 21 and CS Figure 15.**

c) **Please provide scenario analyses, as well as an updated model file including these analyses, using the 'base case' HRs as specified in the clinical effectiveness section of the CS, i.e. those reported in CS Table 20, CS Table 21 and CS Figure 15.**

Response to B9a–c

In Document B.2.9, the results of the ITCs are presented for perioperative durvalumab versus each of the relevant comparators, in order to provide estimates of the relative efficacy of perioperative durvalumab versus each of the relevant comparators for the decision problem.

In the model, EFS for perioperative durvalumab and all comparators (except neoadjuvant PDC) were modelled via applying HRs versus neoadjuvant PDC (extrapolated reference curve), which represented the common comparator in the ITCs. Hence, there are differences between the HRs presented in Document B.2.9 (ITC results) and those presented in Document B.3.3.1 (model inputs), due to the fact that these refer to different comparisons (i.e., durvalumab versus comparators and durvalumab/comparator versus neoadjuvant PDC).

For clarification:

In the base case analysis in the model, the HRs versus neoadjuvant PDC for 3+ months that were used in the piecewise ITC analyses were applied, as described in Document B.3.3.1.

For perioperative durvalumab and neoadjuvant nivolumab + PDC, these piecewise HRs were from the 'base case' MAIC, with the perioperative durvalumab HR representing the treatment effect in the AEGEAN population after weighting to match the CheckMate-816 population more closely:

- EFS HR (95% CI) for perioperative durvalumab versus neoadjuvant PDC: [redacted] – reported in Table 37 in Appendix D.2.2.3

- EFS HR (95% CI) for neoadjuvant nivolumab + PDC versus neoadjuvant PDC: [redacted] – reported in Table 37 in Appendix D.2.2.3

For the 'alternative' base case in the cost-effectiveness analysis, for comparing perioperative durvalumab versus neoadjuvant PDC, surgery alone or adjuvant PDC (based on unadjusted data from AEGEAN, not weighted to match the CheckMate-816 population):

- EFS HR (95% CI) for perioperative durvalumab versus neoadjuvant PDC: [redacted] – reported in Table 37 in Appendix D.2.2.3

For adjuvant PDC and surgery alone, these piecewise HRs were from sensitivity analysis 2 of the NMA (random effects):

- EFS HR (95% CI) for adjuvant PDC versus neoadjuvant PDC: [redacted] – not reported elsewhere in the submission documents

- EFS HR (95% CI) for surgery alone versus neoadjuvant PDC: [redacted] – not reported elsewhere in the submission documents

The preference for sensitivity analysis 2, which excluded two studies from the network (as opposed to the original ITC 'base case' i.e. including all studies), is described in Document B.2.9.2.1 and Appendix D.2.3.4. The results across all comparisons within the NMA (3+ months piecewise) are presented in Table 19.

Hence, the HRs versus neoadjuvant PDC used as model inputs in the cost-effectiveness analysis are based on the preferred (or 'base case') ITC analyses described in Document B.2.9. No additional scenarios have therefore been conducted.

Table 19. EFS NMA results for all comparisons (3+ months piecewise)

Analysis	Treatment effects	HRs				
Base case	Fixed	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
	Random	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 1	Fixed	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]

Analysis	Treatment effects	HRs				
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
	Random	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 2	Fixed	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
	Random	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]

Analysis	Treatment effects	HRs				
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 3	Fixed	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
	Random	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
Sensitivity analysis 4	Fixed	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]

Analysis	Treatment effects	HRs				
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
	Random	Treatment	Adjuvant chemo	Durvalumab	Surgery	Neoadjuvant chemo
		Adjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]
		Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]
		Surgery	[redacted]	[redacted]	[redacted]	[redacted]
		Neoadjuvant chemo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EFS, event-free survival; HR, hazard ratio; NMA, network meta-analysis

In terms of the methods used to derive piecewise HRs versus neoadjuvant PDC from individual trials, patient-level data were first generated for each time interval. Specifically, the data were separated into the respective 0–3 months and 3+ month intervals using the survSplit function in R, through the creation of an indicator variable denoting the timepoint. A Cox regression model with an interaction between the timepoint indicator variable and treatment was then used to obtain an estimate of the piecewise HRs for each trial within the intervals of interest.

For those treatment arms for which individual patient-level data were not available, pseudo individual patient-level data were first derived from the published Kaplan-Meier curves via digitisation and use of the Guyot et al. 2012 algorithm.[54] For the HR for perioperative durvalumab versus neoadjuvant PDC, the unweighted and weighted AEGEAN individual patient-level data were used.

d) The EFS hazard ratio is assumed to be maintained after the observed data from the AEGEAN trial. Please provide detailed justification with supportive evidence for this assumption.

Response

The prediction of improved long-term outcomes with perioperative durvalumab, when compared to neoadjuvant nivolumab + PDC, neoadjuvant nivolumab + PDC, adjuvant PDC and surgery alone is grounded in the value of the perioperative approach. A perioperative regimen can offer a more comprehensive treatment approach when the risk of recurrence is the highest.[44,55-58] The use of IO therapy in the neoadjuvant setting has the advantage of priming the patient's immune system whilst the tumour and any involved lymph nodes are still present prior to surgery.[56] Following resection, continuation of immuno-oncology therapy in the adjuvant setting (as per the perioperative approach) may be beneficial, to consolidate the immune response and suppress/eradicate micrometastases, and thus potentially delay or prevent disease recurrence.[58]A perioperative IO therapy regimen may therefore further improve long-term outcomes, such as EFS, and provide the possibility of cure.

In TA876, clinicians validated the EFS long-term projections (modelled by a constant HR) for neoadjuvant nivolumab + PDC and neoadjuvant PDC.[30] Thus, the EFS

hazard ratio was assumed to be maintained after the observed data from the AEGEAN trial is in line with this.

e) **Please provide scenario analyses, as well as an updated model file including these analyses, assuming waning of the treatment effect on EFS at different time points.**

Response

No relevant data to assume the continuation of the treatment effect are available, thus, these scenario analyses cannot be conducted.

f) **Please provide scenario analyses, as well as an updated model file including these analyses, using the time dependent HRs as provided in response to clarification question A24.**

Response

The derivation of time-dependent HRs was deemed inappropriate, as detailed in response to question A24; consequently, the requested analysis cannot be performed.

B 10. Priority question. According to CS Table 31, EFS and time to death were estimated separately and used to inform the transitions from the event free health state. In the CS it is stated that "*Within each cycle, the probability to transition from EF to LRR (TP1) and from EF to DM (TP2) was calculated based on the estimated probability of an EFS event being either an LRR event or a DM event, having accounted first for the probability of an EFS event being death*". Also TP1 and TP2 were calculated as the non-death EFS event multiplied by the probability of the event being LRR or DM.

a) **Please provide a detailed description, with examples how the non-death EFS event probability was calculated based on the formulae described in CS section B.3.3.2.**

Response

The non-death EFS event is decomposed into two probabilities while the death EFS event comprises one probability. The decomposition means that the EFS event is stratified into different categories, each with its own set of transition probabilities.

Assuming n=2 for non-death EFS (TP1 and TP2) and n=1 for death EFS (TP3), and based on the formulae used in the CS, the formula for calculating the non-death EFS event probability is:

Non-death EFS event probability = hazard TP1 + hazard TP2 / sum(hazard TP1 + hazard TP2 + hazard TP3) * Total probability

In this formula, the hazards associated with the individual non-death EFS transition probabilities (TP1 and TP2) are summed and then divided by the total sum of hazards for all transitions. This ensures that the probability is proportionally distributed based on the cause-specific hazards of each transition within the non-death EFS category.

b) **For estimating "*time to death as first EFS event*" for TP3, other EFS events can be considered competing events. Please provide details as well as accompanying justification for how the "*time to death as first EFS event*" was calculated while accounting for these competing events.**

Response

When estimating the "time to death as first EFS event" for TP3, where death is considered as the first event among various EFS events, competing events arise from other EFS events. Competing events are those that preclude the occurrence of the event of interest, in this case, death as the first EFS event. Here are the details and justification for calculating the "time to death as first EFS event" while accounting for these competing events:

Details

- Event of Interest (EFS Event): Death as the first EFS event (represented by TP3).

- Competing Events: Other EFS events (represented by TP1 and TP2).

In this context, a cause-specific hazard model has been used to estimate hazard rates associated with each event, and the cumulative incidence function is employed to calculate the probability of the event of interest occurring.

As shown above, the formula for calculating the non-death EFS event probability when accounting for competing risks is:

Non-death EFS event probability = hazard TP1 + hazard TP2 / sum(hazard TP1 + hazard TP2 + hazard TP3) * Total probability

The transition probabilities for TP1 (EF → LRR), TP2 (EF → DM) and TP3 (EF → Death) were calculated as follows:

TP1 (EF → LR) = Non-death EFS event multiplied by the probability of the event being LRR

TP2 (EF → DM) = Non-death EFS event multiplied by the probability of the event being DM

TP3 (EF → Death)= max(Time to death as first EFS event, probability of death among the general population in the UK)

Justification:

- In a scenario where multiple events can occur; the competing risks concept is essential for appropriately modelling the probabilities associated with the event of interest. In this case, death as the first EFS event competes with other EFS events.
- The methodology reflects the real-world scenario where a patient may experience different EFS events, and the occurrence of one event may impact the likelihood of experiencing another.
- The use of competing risks analysis provides a statistically rigorous way to estimate the probability of the event of interest while considering the presence of competing events.

c) **Please explain how the "*time to death as first EFS event*" was implemented in the economic analyses, e.g. whether it was added to the non-death EFS event.**

Response

The time to death as first EFS event was implemented in the economic analyses by integrating it into the total calculation of EFS outcomes. This involves considering both death and non-death events in the estimation of overall EFS. The implementation is detailed below:

- The composite outcome for EFS includes both death as the first EFS event (TP3) and other non-death EFS events (TP1 and TP2). This composite outcome captures the time until any of these events occur.
- The economic model uses a competing risks approach to model the different components of the composite EFS outcome. Cause-specific hazard functions are estimated for each event, including death as the first EFS event.
- The CIF is used to calculate the cumulative probability of experiencing the composite EFS outcome over time. It considers both the cause-specific hazard for death as the first EFS event and the cumulative incidence of other non-death EFS events.
- The economic analyses involve time-to-event analysis (survival analysis), to estimate the time until the composite EFS outcome occurs.
- Costs and utilities associated with the composite EFS outcome are incorporated into the economic model. This involves assigning appropriate values to each component of the composite outcome.
- The economic model generates outputs related to the cost-effectiveness of the intervention, considering the integrated EFS outcome.

d) **The probability of the event being LRR or DM was assumed to be constant over time (i.e. time independent). Please provide supporting**

evidence (based on the AEGEAN study data) as well as comprehensive justification for this assumption.

Response

The total number of RECIST recurrence events that had occurred at the time of the EFS IA1 in AEGEAN was low ([redacted]), and analyses have not been conducted to assess how the incidence of recurrence events by site might vary by time. Instead of using the data available from the AEGEAN trial on RECIST recurrence by site, the model incorporates alternative inputs based on recommendations from clinical experts at a UK advisory board.[29] In addition, the model aligns with the simplifying assumption made in TA823[40], maintaining that the proportion of recurrence events (local versus distant) remains constant throughout the model's time horizon, as advised by the clinical experts.

e) **Please provide scenario analyses, as well as an updated model file including these analyses, relaxing the assumption that the probability of the event being LRR or DM is constant over time by:**

   i. **Assuming the probability of the event being LRR increases over time.**

   ii. **Assuming the probability of the event being LRR decreases over time.**

   iii. **Assuming the probability of the event being LRR is 0%.**

   iv. **Assuming the probability of the event being LRR is 100%.**

f) **The probability of the event being LRR or DM was assumed to be treatment independent. Please provide supporting evidence (based on the AEGEAN study data) as well as comprehensive justification for this assumption (extending to all comparators).**

Response

We acknowledge the potential treatment dependence of LRR or DM probabilities. However, the base case approach was preferred due to the absence of relevant

evidence justifying varied probabilities or specific values. UK clinicians in an advisory board indicated a lack of evidence on recurrence rates in this patient group but offered treatment-independent estimates ([redacted] for LRR and [redacted] for DM).[29] These estimates were utilised in the final base case, and the assumption of equivalence was deemed appropriate.

g) **Please provide scenario analyses, as well as an updated model file including these analyses, relaxing the assumption that the probability of the event being LRR or DM is treatment independent.**

Response

As specified above, no data is available for this scenario analyses in this context. In the CS, an alternative scenario was explored using the proportions derived from the AEGEAN study ([redacted]% for LRR and [redacted] % for DM),[33] exhibiting a minimal impact on the results.

B 11. Priority question. According to the CS "The hazard plots' shape favoured adopting piecewise extrapolations from 3 months onward to account for changes in hazards. As can also be seen from the cumulative hazard and smoothed hazard plots specifically, the 3-month time period is a turning point in terms of hazard function and aligns with the planned timing of the first RECIST scan post-randomisation in the AEGEAN trial. To capture changes pre- versus post-surgical assessments, a piecewise extrapolation using a 3-month cut-point (91.3 days) was explored. This approach better accounts for these changes in hazards compared to using standard parametric distributions throughout, as demonstrated in the extrapolated EFS over the trial duration in Appendix M. A"

a) **The EAG agrees (based on CS Appendix M) that the smoothed hazard plots indicate a turning point in terms of hazard function. However, given that this turning point aligns with the planned timing of the first RECIST scan post-randomisation in the AEGEAN trial, it is likely protocol driven and it is questionable whether using a piecewise model (with a Kaplan-Meier curve for the first 3 months) results into**

overfitting to the trial data. The standard parametric models (CS Appendix Figure 22), with a smoother EFS curve that appears less protocol driven, might be a better reflection of clinical practice in England and Wales. Please justify the appropriateness of a piecewise model with a 3-month turning point and that this is representative for clinical practice in England and Wales.

Response

A piecewise approach with a 3-month turning point is appropriate because patients undergo surgery following the completion of 4 cycles of neoadjuvant treatment—equivalent to approximately 3 months for both treatment options (i.e., 3-months corresponds to the timing of the first planned tumour assessment following randomised, which was scheduled to occur after patients had completed neoadjuvant therapy and before surgery the time of the RECIST scan).

In clinical practice it is expected that patients would be assessed for disease progression prior to surgery. If not, the identification of disease progression would likely occur during attempted surgery. Therefore, a turning point at or around the time of surgery is also expected in clinical practice.

b) **Please provide scenario analyses, as well as an updated model file including these analyses, using standard parametric survival curves (as well as HRs estimated from baseline instead of 3+ months) to estimate EFS, particularly using:**

   i. **The Exponential distribution**

   ii. **The Generalised Gamma distribution**

Response

The economic model has been updated to include these additional scenarios. The updated results are presented in the Clarification Appendix.

c) **Please elaborate why a piecewise approach, rather than a spline-based approach was adopted by the company and provided scenario**

analyses with spline models whenever appropriate (as well as an updated model file including these analyses).

Response

Using a piecewise approach is more suitable than a spline-based method since there is no/ limited difference in EFS during the initial 3 months of treatment with either perioperative durvalumab or neoadjuvant PDC. The piecewise model incorporates a HR= 1 for the initial 3 months and allows a HR not equal to 1 for the period beyond 3 months by segmenting the curve. This approach ensures simplicity and facilitates straightforward interpretation. Spline-based models, while flexible, introduce unnecessary complexity when a simpler approach (piecewise) is sufficient and effective.

d) **In the CS it is stated that "the EFS predictions from all models were in line with the observed EFS from AEGEAN, apart from the Gompertz model which overestimates the proportion of patients remaining event free in the long term. Therefore, based on long-term extrapolations, the Gompertz model was not considered appropriate for the base case analyses." Please provide comprehensive justification as well as supporting evidence why the Gompertz model was not considered appropriate.**

Response

Gompertz was not considered appropriate for the base case analyses because it did not provide a good statistical fit (2nd worst fit in terms of Akaike information criterion [AIC] and Bayesian information criterion [BIC]). The clinical experts in a UK advisory board also stated that based on the PACIFIC trial results and TNM classification data,[59,60] the EFS may not be as high as they initially believed.[29] Therefore, the Gompertz was considered to overestimate the 5-year EFS rate (41%) in comparison to the alternative (better fitting) models.

e) **Please provide the range of long-term extrapolations (e.g. for 3, 4, 5, 6, 7, 8, 9 and 10 year EFS) that was considered appropriate by clinicians and/or external evidence reflective of the UK context, for all treatment strategies considered.**

Response

Clinicians were presented with 5-year EFS estimates from 6 months to 5 years in a UK advisory board. The decision not to extend estimates beyond 5 years stemmed from the model's cure assumption, assuming a cure at the 5-year mark. [29] Consequently, patients remaining event-free beyond this period are considered cured and are therefore excluded from long-term analyses.

B 12. EFS is used to inform the transitions from the event free health state to LRR, DM and death. According to the CS, "EFS is defined as the time from randomisation to an event of disease progression that precludes surgery, local or distant recurrence, or death due to any cause". Moreover, in the publication of the AEGEAN trial EFS is defined as "the time to the earliest occurrence of progressive disease that precluded surgery or prevented completion of surgery, disease recurrence [assessed in a blinded fashion by independent central review], or death from any cause"

a) According to the CS, disease-free survival (DFS) was defined as "time from resection until local or distant disease recurrence in the subpopulation of patients who were disease-free following resection, or death due to any cause, whichever occurs first" Please justify the use of EFS, and not DFS, to inform the current model structure and elaborate on the implications.

Response

In AEGEAN, DFS is analysed in the modified resected set (i.e., only includes patients with R0/R1 resection margins, and no evaluable disease on the first scan following surgery), with the time to recurrence or death events measured from the date of surgery. DFS therefore assesses the effect of adjuvant therapy following surgery, and in doing so only evaluates efficacy in a subset of patients included in AEGEAN (i.e., those receiving adjuvant therapy after surgery), and does not include events (e.g., progression or death) leading up to surgery. DFS results should therefore be considered in conjunction with other outcomes (e.g., the proportion of patients receiving surgery and achieving R0/R1). The potential impact of neoadjuvant therapy on recurrence or death after surgery should also be considered

when interpreting the results of DFS in AEGEAN, given the lack of re-randomisation prior to the receipt of adjuvant therapy.

b) Please provide scenario analyses, as well as an updated model file including these analyses, replacing EFS by DFS (as an alternative to inform the transitions from the event-free health state).

Response

Providing these analyses is inappropriate since DFS is not a suitable endpoint for measuring a perioperative treatment, as outlined above.

B 13. Immuno-oncology (IO) retreatment was allowed in the economic model. It is uncertain whether the relative effectiveness of initial IO treatment and IO retreatment would be similar or whether the relative effectiveness of IO retreatment would be diminished compared with initial IO treatment.

a) Please justify the assumption that post-recurrence (i.e. LRR and DM health states) the relative effectiveness of initial IO treatment and IO retreatment is identical.

Response

The sources used to model efficacy in LRR and DM were based on those used in previous NICE appraisals for treatments that are representative of the expected treatment pathway in the UK. For example, the PACIFIC trial (as used in TA798)[61] was used to model efficacy in LRR, and the KEYNOTE trials (as used in TA770, TA683 and TA531)[40,62-64] were used to model efficacy in DM. These were used in part to address concerns in previous NICE appraisals in resectable NSCLC (TA823[40]) that the post-recurrence outcomes were not consistent with those seen in other NSCLC appraisals for the later parts of the treatment pathway.

By using these trials for LRR and DM efficacy (which do not include patients who received prior IO for resectable NSCLC), and applying this to all patients who enter the LRR and DM health states and receive IO, the model implicitly assumes that the efficacy of IO in these health states (for those patients who are eligible to receive IO) is the same, regardless of whether IO was received in the previous health state.

This assumption is also made in TA876,[30] via the one-off application of LYs, QALYs and costs associated with IO (and other treatments) was implemented on entry into the DM health state.

The clinical experts at the UK advisory board did note that the outcomes for patients who experience recurrence and enter the LRR or DM health state will have different (and most likely worse) outcomes compared to those who are diagnosed with more advanced stages disease and enter the treatment pathway at these later lines. However, they also noted a lack of evidence for post-recurrence outcomes for patients who might receive IO as a treatment for resectable NSCLC, including those who might receive subsequent IO.[29] In the absence of evidence however, they considered the sources used in the model for LRR and DM efficacy to be overall reasonable.

b) Please provide scenario analyses, as well as an updated model file including these analyses, assuming that post-recurrence, the relative effectiveness of IO retreatment would be diminished compared with initial IO treatment.

Response

It is not appropriate to conduct these analyses since there is no direct evidence available.

c) Please provide scenario analyses, as well as an updated model file including these analyses, assuming all potentially eligible patients receive IO retreatment post-recurrence (i.e. assuming that the IO treatment proportions for perioperative durvalumab and neoadjuvant nivolumab + PDC are identical as for neoadjuvant PDC).

Response

The economic model has been updated to include these scenario analyses.

B 14. According to CS Figure 20, the state-transition model includes six transition probabilities. However, in the clinical inputs section of CS Table 83, more than 6 inputs/parametric models are provided. Please provide an overview of the CS Table 83 clinical inputs section (used in the base-case),

organised per transition probability (as per CS Figure 20). In case multiple clinical inputs are provided per transition probability, then please specify what is exactly estimated and how the different clinical inputs are combined.

Response

Table 20. Overview of clinical inputs (used in the base-case), organised per transition probability

Transition probability	Description	Parametric model
TP1	EF → LRR (Analysis of AEGEAN data (assumed to account for [redacted] of the non-death EFS events based on KOL feedback))	Log-normal
TP2	EF → DM (Analysis of AEGEAN data (assumed to account for [redacted] of the non-death EFS events based on KOL feedback))	Log-normal
TP3	EF → Death (Analysis of AEGEAN data (from EFS; time to death as first EFS event))	Log-normal
TP4	LRR → DM (Based on PACIFIC trial (TTP), as used in TA798)[65]	Generalised gamma
TP5	LRR → Death a (Based on PACIFIC trial (difference in PFS and TTP), as used in TA798) [65]	Generalised gamma OS after LRR from Wong et al. 2016[43]: Log-logistic
TP6	DM → Death (Based on KEYNOTE trials for pembrolizumab (with or without chemotherapy) (PFS and OS) across relevant populations (KEYNOTE-024, KEYNOTE-189 and KEYNOTE-407),[66-68] as used in TA531, TA683 and TA770.[62-64] PFS and OS included in nested partitioned survival model approach)	KEYNOTE-024 PFS (Pembro arm): Log-logistic[68] KEYNOTE-189 PFS (Pembro + CT arm): Log-normal[66] KEYNOTE-407 PFS (Pembro + CT arm): Log-logistic[67] KEYNOTE-189 PFS (Placebo + CT arm): Log-normal[66] KEYNOTE-407 PFS (Placebo + CT arm): Log-logistic[67] KEYNOTE-024 OS (Pembro arm): Log-normal[68] KEYNOTE-189 OS (Pembro + CT arm): Log-logistic[66] KEYNOTE-407 OS (Pembro + CT arm): Log-logistic[67]

		KEYNOTE-189 OS (Placebo + CT arm): Log-logistic[66] KEYNOTE-407 OS (Placebo + CT arm): Log-logistic[67] OS after DM from Wong et al. 2016: Log-logistic[43]

Abbreviations: DM, distant metastasis; EF, event-free; LRR, locoregional recurrence; OS, overall survival; PFS, progression-free survival; TP, transition probability

Health-related quality of life

B 15. Priority question. HRQoL data collected in the AEGEAN trial were analysed using mixed models for repeated measures (MMRM) to estimate the statistical relationship between utilities and health state (defined by recurrence or treatment status).

a) Please provide, per measurement timepoint and treatment arm:

i. The total number of EQ-5D responses

ii. The estimated mean utility and standard error

iii. A breakdown of how many patients were event-free and had an event

iv. A breakdown of how many patients were on and off treatment and the respective utility scores

v. The extent of missing data observed

Response

Tables including the requested information are provided below:

Table 21. Utility summary statistics

Treatment	Scenario	Subjects	Observations	Mean (SD)	Median (IQR)	Min	Max
Placebo + SoC	At baseline visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab + SoC	At baseline visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + SoC	All visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab + SoC	All visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled treatments	Pre-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled treatments	Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + SoC	Pre-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + SoC	Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab + SoC	Pre-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab + SoC	Post-recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + SoC	Unknown status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab + SoC	Unknown status	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IQR, inter quartile range; SD, standard deviation; SoC, standard of care

Table 22. Compliance with EQ-5D by visit – neoadjuvant and adjuvant periods (mITT population)

Timepoint	Compliance	Perioperative durvalumab n=366	Perioperative placebo n=374
Neoadjuvant			
Baseline	Expected forms n	[redacted]	[redacted]
	Compliance rate %	[redacted]	[redacted]
	Expected forms missing n (%)	[redacted]	[redacted]
	Technical problems with device %	[redacted]	[redacted]
	Other %	[redacted]	[redacted]
	Missing reason %	[redacted]	[redacted]
Week 3	Expected forms	[redacted]	[redacted]
	Compliance rate %	[redacted]	[redacted]
	Expected forms missing n (%)	[redacted]	[redacted]
	Technical problems with device %	[redacted]	[redacted]
	Too sick, other than disease under investigation %	[redacted]	[redacted]
	Administrative failure to distribute questionnaire to subject %	[redacted]	[redacted]
	Illiterate %	[redacted]	[redacted]
	Other %	[redacted]	[redacted]
	Missing reason %	[redacted]	[redacted]
Week 6	Expected forms n	[redacted]	[redacted]
	Compliance rate %	[redacted]	[redacted]
	Expected forms missing n (%)	[redacted]	[redacted]
	Technical problems with device %	[redacted]	[redacted]
	Administrative failure to distribute questionnaire to subject %	[redacted]	[redacted]
	Illiterate %	[redacted]	[redacted]
	Other %	[redacted]	[redacted]
	Missing reason %	[redacted]	[redacted]
Week 9	Expected forms n	[redacted]	[redacted]
	Compliance rate %	[redacted]	[redacted]
	Expected forms missing n (%)	[redacted]	[redacted]
	Technical problems with device %	[redacted]	[redacted]
	Too affected by symptoms of disease under investigation %	[redacted]	[redacted]
	Administrative failure to distribute questionnaire to subject %	[redacted]	[redacted]
	Illiterate %	[redacted]	[redacted]
	Other %	[redacted]	[redacted]
	Missing reason %	[redacted]	[redacted]

Week 12	Expected forms n Compliance rate % Expected forms missing n (%) Technical problems with device % Administrative failure to distribute questionnaire to subject % Illiterate % Other % Missing reason %	[redacted]	[redacted]
Adjuvant			
Baseline	Expected forms n Compliance rate % Expected forms missing n (%) Administrative failure to distribute questionnaire to subject % Illiterate % Missing reason %	[redacted]	[redacted]
Neoadjuvant follow-up*			
Day 30	Expected forms n Compliance rate % Expected forms missing n (%) Too affected by symptoms of disease under investigation % Missing reason %	[redacted]	[redacted]
Month 2	Expected forms n Compliance rate % Expected forms missing n (%) Too affected by symptoms of disease under investigation % Other % Missing reason %	[redacted]	[redacted]
Month 3	Expected forms n Compliance rate % Expected forms missing n (%) Administrative failure to distribute questionnaire to subject % Other % Missing reason %	[redacted]	[redacted]
Month 6	Expected forms n Compliance rate % Expected forms missing n (%) Unwilling %	[redacted]	[redacted]

	Too affected by symptoms of disease under investigation % Administrative failure to distribute questionnaire to subject % Other % Missing reason %	[redacted]	[redacted]
Adjuvant follow up*			
Day 30	Expected forms n Compliance rate % Expected forms missing n (%) Administrative failure to distribute questionnaire to subject % Other % Missing reason %	[redacted]	[redacted]
Month 2	Expected forms n Compliance rate % Expected forms missing n (%) Technical problems with device % Administrative failure to distribute questionnaire to subject % Other % Missing reason %	[redacted]	[redacted]
Month 3	Expected forms n Compliance rate % Expected forms missing n (%) Unwilling % Missing reason %	[redacted]	[redacted]
Month 6	Expected forms n Compliance rate % Expected forms missing n (%) Technical problems with device % Other % Missing reason %	[redacted]	[redacted]
Overall subject compliance	Expected forms n Compliance rate %	[redacted]	[redacted]
Overall**	Compliance rate %	[redacted]	[redacted]

*Includes those who completed/discontinued treatment

**Total number of evaluable questionnaires across all timepoints divided by total number of questionnaires expected to be received across all timepoints *100.

b) **Please explain, with appropriate justification, how missing data were handled and the implications of this approach.**

Response

Missing data was not imputed for the utility analysis for the MMRM modelling and was treated as though it was missing at random (MAR) – as per the assumptions when fitting an MMRM model.

c) **Please clarify what the likely causes of missing data were and what the potential impact of these missing data on the estimation of the utility scores would be, separately for patients who had completely and partially missing utility data.**

Response

In relation to the impact of missing data in EQ-5D collection, it's challenging to provide a definitive assessment. However, it's important to note that our analysis doesn't assume differences in treatment arms for the EF utility value. The data is solely utilised to inform the EF health state and is not extended to later health states or post-progression stages, where compliance might naturally decline over time.

While acknowledging the potential limitations due to missing data, it's worth highlighting that assuming higher utility values may not be plausible given that the current values are already higher than the UK general population norms. To address this uncertainty and explore variations in utility, we conducted scenario analyses and a one-way sensitivity analysis (sections B.3.9.2 and B.3.9.3 in the CS).

Furthermore, we tested a lower utility value for EF using Andreas et al. 2018,[69] resulting in an approximate 23% increase from the base case ICER for all comparators. While this represents a modest increase, it provides insights into the potential impact of lower utility values on the cost-effectiveness results. We consider these analyses, including the sensitivity testing, to offer a thorough exploration of the uncertainties associated with utility values in the cost-effectiveness model.

d) **Please provide full details of all mixed effects models that were considered, including diagnostics, specification of covariance structures, candidate covariates and results.**

Response

Methods

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-5L health state utilities.[70] The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Recurrence status (pre-recurrence, post-recurrence)
- Treatment + Recurrence status
- Treatment + Recurrence status + Treatment * Recurrence status (Both terms and their interaction included)

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. These models using the first covariance structure in the sequence successfully converged for all models (i.e., for each of the 4 covariate options). If for a particular set of covariates none of the models converged, then no results were presented for that model, and the remaining model results were based on the most flexible covariance structure for which the models converged.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

- Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
- Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
- Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
- Toeplitz – as above for number 2, but each visit shares the same variance.
- Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

For each model, parameter estimates, and marginal ('least square') means are presented below including 95% confidence intervals. The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (treatment and/or Recurrence status) that is averaged over observations and with adjustment for repeated measures. Analysis was performed in R 4.1.0 using the mmrm package 0.2.2 for model fitting.

Results

In total, 3590 EQ-5D-5L observations were available from 699 patients. Of these, 3475 observations were recorded pre-recurrence, 115 were recorded post-recurrence and 63 were recorded after censoring for recurrence (see utility summary statistics table in response to question a) iv).

The results presented below were generated from MMRMs with the following covariance structure: Toeplitz with Heterogeneity.

Table 23. Goodness of fit

Description	converges	AIC	BIC
Treatment	TRUE	-4103.9	-4017.6
Recurrence status	TRUE	**-4142.1**	-4055.8
Treatment + Recurrence status	TRUE	-4136.8	-4050.4
Treatment * Recurrence status	TRUE	-4137.1	-4050.8

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

The best fitting model in terms of AIC was the model including a term for Recurrence status. Therefore, 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.

The following tables contain summaries of the point estimates and marginal means produced from each model.

Table 24. Summary of point estimates

Parameter	Treatment	Recurrence status	Treatment + Recurrence status	Treatment * Recurrence status
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab + SoC	[redacted]		[redacted]	[redacted]
Post-recurrence		[redacted]	[redacted]	[redacted]
Durvalumab + SoC: Post-recurrence				[redacted]
AIC score	-4103.9	-4142.1	-4136.8	-4137.1

Abbreviations: AIC, Akaike information criterion; SoC, standard of care

Table 25. Summary of marginal mean

Parameter	Treatment	Recurrence status	Treatment + Recurrence status	Treatment * Recurrence status
Placebo + SoC	[redacted]			
Durvalumab + SoC	[redacted]			
Pre-recurrence		[redacted]		
Post-recurrence		[redacted]		
Placebo + SoC:Pre-recurrence			[redacted]	[redacted]
Durvalumab + SoC:Pre-recurrence			[redacted]	[redacted]
Placebo + SoC:Post-recurrence			[redacted]	[redacted]
Durvalumab + SoC:Post-recurrence			[redacted]	[redacted]
AIC score	-4103.9	-4142.1	-4136.8	-4137.1

Abbreviations: AIC, Akaike information criterion; SoC, standard of care

B 16. Priority question. A summary of the health state utility values was provided in Table 49 of the CS. The utility value for the EF health state was estimated using HRQoL data collected in the AEGEAN trial (DCO 10 November 2022). The LRR health state utility was sourced from TA798 using EQ-5D data from PACIFIC, whereas utility values for the DM1 and DM2 health states were sourced from TA683 using EQ-5D data from KEYNOTE-189.

a) According to the CS, the utility value for the EF health state was informed by AEGEAN data of the neoadjuvant period (week 12) only. Please elaborate on the potential implications of not using AEGEAN data of the adjuvant period for the estimation of the EF health state utility value.

Response

We appreciate that there may be potential implications of not using AEGEAN data from the adjuvant period for estimating the EF health state utility value. For instance, a limited representation of overall health-related quality of life, potential oversight of the varying observed effects at different points in time, and the risk of underestimating or overestimating the treatment's impact.

However, the utility values weren't derived from the adjuvant period due to collection limitations, as they were only gathered during the adjuvant baseline visit and the post-discontinuation follow-up visit, excluding the rest of the adjuvant treatment visits.

b) **In Section 3.4.1.3 of the CS it is stated that "Due to low number of observations recorded post-recurrence, the same utility values to the EF health state were used for the LRR health state". This statement seems to contradict the utility values as reported in CS Table 49, in which the LRR utility differs from the EF utility and was sourced from TA798. Please provide clarification for this.**

Response

This is an error in the CS. The utility value for the LRR health state is sourced from TA798 to align with the PACIFIC trial.[65]

c) **Please provide full details of how the utility values reported in CS Table 49 for the EF, LRR, DM1 and DM2 were derived, including comparisons of the PICO (population, intervention, comparator(s), outcome(s)) of the used studies and the analyses performed.**

Table 26. PICO of used studies to derive the health state utility values.

Trial	Health state	Population	Intervention	Comparator	Outcome
AEGEAN	EF	Resectable NSCLC	Perioperative durvalumab + PDC	Perioperative placebo + PDC	Primary outcome: EFS
PACIFIC EQ-5D (as per TA798)	LRR	Stage III (locally advanced),	CRT followed by durvalumab	Placebo	Primary outcomes: PFS and OS

		unresectable NSCLC			
KEYNOTE-189 EQ-5D (as per TA683)	DM1	First Line Metastatic Non-squamous NSCLC	Pembrolizumab + pemetrexed/platinum chemotherapy	Placebo + pemetrexed/platinum chemotherapy	Primary outcomes: PFS and OS
KEYNOTE-189 EQ-5D (as per TA683)	DM2	First Line Metastatic Non-squamous NSCLC	Pembrolizumab + pemetrexed/platinum chemotherapy	Placebo + pemetrexed/platinum chemotherapy	Primary outcomes: PFS and OS

Abbreviations: CRT, chemoradiotherapy; DM, distant metastasis; EF, event-free; LRR, locoregional recurrence; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PICO, Patient, Intervention, Comparator, Outcomes; TA, technology appraisal

d) Please provide justification for the selected sources to inform the utility values for the LRR, DM1 and DM2 health states.

Response

The utility values selected for analysing LRR and DM were derived from relevant clinical trials that have been utilised in the survival analysis of these specific health states presented in the CS. This ensures consistency with the sources employed in both the survival analysis and utility assessment. In addition, NICE has previously accepted these trials as suitable for modelling utilities in the relevant health states.

e) Please provide an updated economic model and scenario analyses modelling the LRR, DM1 and DM2 health state utilities as utility decrements to the EF utility informed by the AEGEAN trial.

Response

The health state utility values used in the base case are utility decrements to the EF utility (see Table 27). As patients experience disease progression through the model, the utility in each subsequent health state decreases compared to the utility that patients experience when first entering the event-free state.

Table 27. Health state utilities

Utility	Value
Utility EF	[redacted]
Utility LRR	[redacted]
Utility: DM1 (pre-progression)	0.759
Utility: DM2 (post-progression)	0.662

Abbreviations: DM, distant metastasis; EF, event-free; LRR, locoregional recurrence

f) Please cross validate the health state utility values in CS Table 49 with other relevant TAs and provide scenario analyses using these to inform health state utilities in the economic model.

Response

TA876 is the most relevant submission, however the utility values have been redacted from the submission, therefore it is not possible to cross validate.[30] Similarly, in TA761 the DFS (and LRR) and DM1 utility values have been redacted from the submission. However, AstraZeneca has gained internal access to the ADAURA and FLAURA utility values, which are presented below, but these remain confidential and have been redacted.

Table 28. TA761 and TA823 utility values per health state

TA	Health state	Utility value	Source
TA823[40] (Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer)	DFS	0.80	Jang et al. 2010[71]
	LRR	0.77	Chouaid et al. 2013[72]
	1st line metastatic recurrence	0.71	IMpower150
	2nd line metastatic recurrence	0.69	Nafees et al. 2008[73]
TA761[49] (Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection)	DFS	[redacted]	ADAURA utility analysis
	LRR	[redacted]	Assumed to be same as for DFS
	Distant metastasis 1	[redacted]	FLAURA utility analysis
	Distant Metastasis 2	0.640	Labbé et al. 2017[74]

Abbreviations: DFS, disease-free survival; LRR, locoregional recurrence; TA, technology appraisal

Scenario analyses have been conducted using the utility values from TA823 and TA761.

Adverse events

B 17. The cost-effectiveness model takes into account grade 3 or 4 AEs which occurred in more than 5% of patients during the neoadjuvant and/or adjuvant treatment phases in the AEGEAN trial. AE costs and disutilities were applied as a one-off cost/disutility in the first cycle of the economic model.

a) Please provide an updated economic model and scenario analysis including all grade 3+ AEs during the neoadjuvant and/or adjuvant treatment phases in the AEGEAN trial, regardless of the percentage of patients in which these occurred.

Response

The economic model has been updated to include grade 3 or 4 AEs which occurred in more than 1% (instead of 5%) of patients during the neoadjuvant and/or adjuvant treatment phases in AEGEAN. The 1% threshold was deemed appropriate as the inclusion of all grade 3+ AEs in AEGEAN (and comparator trials for non-AEGEAN comparators) would lead to a great number of additional AEs, which would overcomplicate the model and the assumptions required for costs and disutilities related to AEs. Including AEs of grade 3-4 that occurred in >1% of patients is a conservative approach, that would only have a small impact on the results.

Thus, based on the 1% threshold, 7 AEs were added on top of neutropenia, neutrophil count decreased and anaemia. These are: leukopenia, white blood cell count decreased, platelet count decreased, thrombocytopenia, vomiting, asthenia and decreased appetite. The first 6 AEs were included as they exceeded the 1% threshold in the AEGEAN trial, whereas decreased appetite was reported in the neoadjuvant nivolumab + PDC arm in CheckMate-816 in >1% of patients.

Following the requested updates on this section, we reviewed the input parameters and calculations throughout the “AEs” tab. A few minor errors were identified which have been corrected in the updated economic model. The updates have a minor impact on the results. An overview of the AEs included and associated disutilities is presented in Table 29.

The updates include:

4. In Cells M and N 32:33 the CHOOSE formula has been corrected, as due to a typo, no value could be assigned to [value 3], i.e., when the selected comparator was adjuvant PDC.

5. The percentage of patients receiving neutropenia in the perioperative durvalumab arm (from 8.7% to 9.0% - "AEs" tab, Cell E31), to be exactly aligned with Heymach et al. 2023.[18]

6. The calculation of QALY losses per treatment arm in the model to be divided by days per month instead of days per week ("Utilities" tab, Cells E54-56), as this assumption was overestimating the total QALY losses.

Table 29. AE disutility values

Adverse event	Disutility	Source
Neutropenia	-0.007	Nafees et al. 2008 - as per TA876[73]
Neutrophil count decreased	-0.007	Assumed the same as neutropenia
Anaemia	-0.007	Assumed the same as neutropenia - as per TA876[30]
Leukopenia	-0.007	Assumed the same as neutropenia
White blood cell count decreased	-0.007	Assumed the same as neutropenia - as per TA876[30]
Platelet count decreased	-0.007	Assumed the same as neutropenia
Thrombocytopenia	-0.007	Assumed the same as neutropenia
Vomiting	-0.004	Nafees et al. 2008 - as per TA876[73]
Asthenia	-0.006	Nafees et al. 2008 - as per TA876[73]
Decreased appetite	-0.004	TA653[75] - as per TA761[49]

Abbreviation: AE, adverse event; TA, technology appraisal

b) Please comment on the reversibility and duration of the modelled AEs, i.e. provide justification for the assumption that the duration of each AE was one month for all AEs irrespective of therapy.

Response

There are no available data from the AEGEAN trial regarding the duration of AEs, thus, for simplicity, duration of one month has been assumed. Although this is certainly a limitation of the model, the impact of this limitation is expected to be minor.

Healthcare resource use and costs

B 18. Priority question. Post recurrence (i.e., LRR and DM health states), retreatment with IO is expected for patients who have received IO as an adjuvant or neoadjuvant therapy in the resectable setting and have not progressed within 6 months since completing previous IO treatment.

a) Please provide the proportion of patients receiving IO post recurrence that did not initially receive IO treatment.

Response

As confirmed with the EAG in the clarification call, a table including the proportion of patients receiving IO in the LRR and DM health states following **IO treatment in the EF state** are provided in Table 30. This information is also provided in Tables 64, 69 and 70 for LRR, DM1 and DM2, respectively, in the CS.

Table 30. Proportion of patients receiving IO post recurrence following IO treatment in the EF health state

	LRR	DM1	DM2
Proportion receiving IO following **IO treatment** in the EF state	37.1%	61.9%	11.1%

Abbreviations: DM, distant metastasis; IO, immuno-oncology; LRR, locoregional recurrence

b) **Please provide the proportion of patients receiving IO post recurrence that did not initially receive IO treatment**.

Response

As confirmed with the EAG in the clarification call, a table including the proportion of patients receiving IO in the LRR and DM health states following **no IO treatment in the EF state** are provided in Table 31. This information is also provided in tables 64, 69 and 70 for LRR, DM1 and DM2, respectively, in the CS.

Table 31. Proportion of patients receiving IO post recurrence following no IO treatment in the EF health state

	LRR	DM1	DM2
Proportion receiving IO following **no IO treatment** in the EF state	37.1%	61.9%	11.1%

Abbreviations: DM, distant metastasis; IO, immuno-oncology; LRR, locoregional recurrence

c) Please provide an overview of the proportions of patients receiving IO retreatments per treatment arm.

Response

See sections B.3.3.4.1 and B.3.3.5.1 in the CS for further details on the proportion of patients receiving IO retreatment in the LRR and DM health states, respectively (see Table 32).

Table 32. Proportion of patients receiving IO retreatments per treatment arm

	Proportion receiving IO retreatment in LRR	Proportion receiving IO retreatment in DM
Perioperative durvalumab	46.6%	80%
Neoadjuvant PDC	46.6%	80%
Neoadjuvant nivolumab + PDC	46.6%	80%
Adjuvant PDC	46.6%	80%
Surgery alone	46.6%	80%

Abbreviations: DM, distant metastasis; IO, immuno-oncology; LRR, locoregional recurrence

d) Please provide supporting evidence and justification for using a 6-month cut-off.

Response

As stated in the CS, this assumption is in line with clinical feedback that was received in previous HTA submissions in early-stage NSCLC (TA823 and TA876).[30,49] In addition, this assumption was validated by UK clinical experts in an advisory board.[29]

e) Please provide an updated economic model and scenario analyses using alternative cut-off time points.

Response

Based on clinical feedback in an UK advisory board, a scenario including an alternative cut-off time point of 1 year has been incorporated in the model. The updated results are presented in the Clarification Appendix.

B 19. Priority question. Table 54 shows the distribution of PDC in the neoadjuvant setting in the intervention and comparator arms. Shares of PDC treatments for the perioperative durvalumab arm and neoadjuvant PDC arms were informed by distributions in AEGEAN clinical study report (CSR) Table 14.3.1.1.3. For neoadjuvant nivolumab + PDC, the share of PDC was informed by CheckMate-816. Further, CS Table 55 suggests nivolumab costs in the neoadjuvant nivolumab +PDC arm are derived from the durvalumab TDT in the AEGEAN perioperative durvalumab arm.

a) Please provide evidence to justify shares utilised for perioperative durvalumab +PDC and neoadjuvant PDC from AEGEAN being reflective of UK clinical practice.

Response

The shares utilised for perioperative durvalumab + PDC and neoadjuvant PDC were informed by the distribution of chemotherapy regimens in AEGEAN.[18] Based on insights from a UK advisory board, clinical experts confirmed that carboplatin is relevant in resectable NSCLC as a platinum agent for platinum-based chemotherapy and may be seen in UK clinical practice more frequently than cisplatin. This is reflected in the CS, where it is assumed that 73% and 74% of patients in the perioperative durvalumab + PDC and neoadjuvant PDC arms, accordingly, received carboplatin-based PDC. Whereas only 27% and 26% patients in the perioperative durvalumab + PDC and neoadjuvant PDC arms, accordingly, received cisplatin-based PDC. The clinical experts agreed that the AEGEAN trial was generalisable to UK clinical practice.

b) Please provide evidence to justify shares utilised for neoadjuvant nivolumab +PDC from CheckMate-816 being reflective of clinical practice in England and Wales.

Response

Due to the lack of direct evidence, the allocation of shares for neoadjuvant nivolumab + PDC relied on data from the CheckMate-816 study publication and trial permissions based on patient characteristics like squamous/ non squamous histology. According to Forde et al. 2022,[7] Carboplatin + Paclitaxel was the only planned carboplatin regimen, administered to 21.8% of patients. Specific regimens like Cisplatin + Gemcitabine for squamous histology and Cisplatin + Pemetrexed for non-squamous histology were defined. We acknowledge that in TA876 the EAG had some concerns regarding the distribution of carboplatin and cisplatin-based PDC regimens, however, in the absence of data to inform the PDC landscape in clinical practice in England and Wales, the CS followed a conservative approach, relying on the available data from CheckMate-816. It was therefore deemed appropriate for use in this CS.

c) **Please provide justification for calculating nivolumab costs in the neoadjuvant setting based on durvalumab TDT from the AEGEAN perioperative durvalumab arm.**

Response

Data for TDT covers both the neoadjuvant and adjuvant treatment phases. Consequently, inputs for the duration of neoadjuvant and adjuvant treatments determine the appropriate cycle where the relevant costs were allocated. For outside-trial comparators, assumptions were made to model the TDT. The durvalumab TDT from the AEGEAN perioperative durvalumab arm was used to calculate the nivolumab costs in the neoadjuvant setting, as a simplifying approach to account for the lack of evidence for nivolumab TDT. Durvalumab TDT was used for nivolumab costs, assuming that this TDT data would represent TDT for IO treatments. In addition, differences in the number of neoadjuvant treatment cycles between AEGEAN and CheckMate-816 were captured by the respective neoadjuvant treatment duration inputs.

B 20. Priority question. CS section 3.5.2.1.2 provides treatment acquisition costs for adjuvant treatments. Table 56 presents the proportion of patients in the neoadjuvant nivolumab +PDC arm receiving adjuvant treatments. Table 57 presents the PDC treatment shares for nivolumab

+PDC and adjuvant PDC, with the latter assuming an equal split. It is unclear to the EAG where these table inputs were derived. Further, whilst table 56 suggests 63.6% in the nivolumab +PDC arm received adjuvant PDC, Table 57 states that 74.3% received a PDC regimen.

a) Please specify where the table inputs for Tables 56 and 57 of the CS can be found.

Response

The inputs for Tables 56 and Table 57 of Document B (for nivolumab + PDC) are based on the published data from Forde et al. 2022 (CheckMate-816 publication). In the Supplementary Appendix, it is reported that 9/35, i.e., 25.7% patients in the Nivolumab arm received RT alone as adjuvant therapy.[7] In addition, according to the same publication, 42.3% patients receiving adjuvant chemotherapy in the Nivolumab arm received carboplatin, therefore of those receiving adjuvant chemotherapy (100% - % RT = 74.3%), 42.3% = Carboplatin + Paclitaxel (as only planned carboplatin regimen); of the remaining 57.7%, an equal split between Cisplatin + Docetaxel; Cisplatin + Gemcitabine; Cisplatin + Pemetrexed and Cisplatin + Vinorelbine was assumed. This simplifying assumption was undertaken due to lack of data to support the distribution of cisplatin regimens. The impact of this assumption on the results is expected to be minor. Sources are now presented in Table 33.

Table 33. PDC treatments received in the adjuvant setting

PDC type		Nivo + PDC[a]	Source	Adjuvant PDC	Source
Cisplatin +	Pemetrexed	10.7%	Forde et al. 2022 and equal distribution across cisplatin regimens has been assumed[7]	11.1%	Equal distribution has been assumed
	Vinorelbine	10.7%		11.1%	
	Gemcitabine	10.7%		11.1%	
	Docetaxel	10.7%		11.1%	
Carboplatin +	Pemetrexed	31.5%	Forde et al. 2022[7]	11.1%	
	Paclitaxel	0.0%		11.1%	
	Gemcitabine	0.0%		11.1%	
	Vinorelbine	0.0%		11.1%	
	Docetaxel	0.0%		11.1%	

Abbreviations: PDC, platinum-doublet chemotherapy.
[a] In this arm, 25.7% of those receiving adjuvant treatment is receiving radiotherapy and the rest (74.3%) one of the PDC regimens listed above

b) Please clarify why there is a discrepancy in the reported proportion in the nivolumab +PDC arm receiving adjuvant PDC.

Response

Table 34 is now in line with Table 57 of Document B. As 25.7% is expected to receive adjuvant radiotherapy in the neoadjuvant nivolumab + PDC arm, the remainder of patients (i.e., 74.3%) will receive PDC treatments.

Table 34. Proportion of patients in the neoadjuvant nivolumab + PDC arm receiving adjuvant treatments

Treatment	% receiving adjuvant treatment	% receiving adjuvant systemic therapy (PDC)	% receiving adjuvant radiotherapy	Source
Neoadjuvant nivolumab + PDC	19.9%	74.3%	25.7%	Forde et al. 2022[7]

Abbreviations: PDC, platinum-doublet chemotherapy.

c) Please provide evidence to support the share of PDC treatments in the adjuvant PDC arm being equally divided.

Response

This simplifying assumption was undertaken due to lack of data to support the distribution of PDC regimens. The impact of this assumption on the results is expected to be minor.

d) As per CS Table 58, PDC costs in the adjuvant setting for the neoadjuvant nivolumab +PDC and adjuvant PDC arms were derived from the neoadjuvant PDC TDT for the AEGEAN perioperative placebo arm. Please provide justification and supporting evidence as to the plausibility of this assumption.

Response

Data for TDT covers both the neoadjuvant and adjuvant treatment phases. As discussed in B.19.c for non-trial comparators, assumptions were made to model the TDT. The neoadjuvant PDC TDT from the AEGEAN perioperative placebo arm was used to calculate PDC costs in the adjuvant setting for the neoadjuvant nivolumab + PDC and adjuvant PDC comparator arms. This assumption was made based on the

assumption that the TDT data from the neoadjuvant PDC in the placebo arm would provide a more accurate representation of TDT for non-IO treatments. To account for the differences in timing between the neoadjuvant PDC TDT and its use to inform adjuvant PDC, TDT was recalibrated from the time that adjuvant PDC starts. This recalibration was conducted in accordance with the percentage of patients remaining in the EF health state during that specific cycle (Table 58, Document B).

B 21. No AE costs were assumed to be present for surgery alone. This was justified through the approach taken in TA876. Please provide further justification as to the plausibility of this assumption.

Response

Based on TA876, the economic model does not assume any AE costs for surgery alone.[30] This is a relatively strong assumption but mean that the results presented in the base case are conservative in nature.

B 22. For monitoring costs, one test was assumed per treatment cycle (21 days) for the event free health state. This was justified through key opinion leader validation. In LRR and DM health states, four tests were assumed in the model per treatment cycle. No justification was provided for this assumption. Please provide justification for assuming four tests per treatment cycle for liver function tests, renal functions tests, and complete blood count.

Response

TA876 included four tests per treatment cycle for liver function tests, renal functions tests, and complete blood count for the LRR health state.[30] Therefore, the CS aligned with this approach.

B 23. Vial sharing was included in the CS base case for chemotherapy costs to exclude wastage. Although CS Table 84 suggests that a no vial sharing scenario analysis was explored, this scenario analysis was not reported in CS section B.3.9.3. Please provided a scenario analysis and updated economic model with no vial sharing for chemotherapy.

Response

The economic model has been updated with this scenario analysis.

B 24. CS Table 59 presents dosing regimens per cycle in the EF health state. Please provide detail regarding how dosages per administration were derived for PDC treatments. Please highlight differences with those found in TA876 and provide justification for differences in the included doses.

Response

The dosages per administration for PDC treatments was informed by the respective SmPC. Table 59 of the CS presents the dose per administration per unit, after the dosing calculations, e.g., mg/mL/min for GFR, mg/m2 for BSA. Table 35 presents the dosing per administration as reported in the SmPC and is now in line with TA876.[30]

Table 35. Dosing regimen per cycle in EF health state

Treatment in EF health state		Dose per administration		Frequency (per treatment cycle) [a]	Max administrations
Perioperative durvalumab (Neoadjuvant phase)	Durvalumab +	1500.0	mg	1	4
	Carboplatin	5	mg/mL/min	1	
	Pemetrexed	500	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Cisplatin	75	mg/m^2	1	
	Pemetrexed	500	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Carboplatin	6	mg/mL/min	1	
	Paclitaxel	200	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Carboplatin	5	mg/mL/min	1	
	Gemcitabine	1250	mg/m^2	2	
	Durvalumab +	1500.0	mg	1	4
	Cisplatin	75	mg/m^2	1	
	Paclitaxel	200	mg/m^2	1	
	Durvalumab +	1500.0	mg	1	4
	Cisplatin	75	mg/m^2	1	
	Gemcitabine	1250	mg/m^2	2	
Neoadjuvant nivolumab + PDC	Nivolumab +	360.0	mg	1	3
	Cisplatin	75	mg/m^2	1	
	Pemetrexed	500	mg/m^2	1	

	Nivolumab +	360.0	mg	1	3
	Carboplatin	5	mg/mL/min	1	
	Paclitaxel	200	mg/m^2	1	
	Nivolumab +	360.0	mg	1	3
	Cisplatin	75	mg/m^2	1	
	Gemcitabine	1250	mg/m^2	2	
Perioperative durvalumab (adjuvant phase)	Durvalumab	1500.0	mg	1	12
PDC [b, c]	Carboplatin +	5	mg/mL/min	1	4 (neoadj) 3 (adj)
	Pemetrexed	500	mg/m^2	1	
	Cisplatin +	75	mg/m^2	1	4 (neoadj) 3 (adj)
	Pemetrexed	500	mg/m^2	1	
	Carboplatin +	6	mg/mL/min	1	4 (neoadj) 3 (adj)
	Paclitaxel	200	mg/m^2	1	
	Cisplatin +	75	mg/m^2	1	4 (neoadj) 3 (adj)
	Gemcitabine	1250	mg/m^2	2	
	Cisplatin +	75	mg/m^2	1	4 (neoadj) 3 (adj)
	Paclitaxel	200	mg/m^2	1	
	Cisplatin +	75	mg/m^2	1	3 (adj)
	Vinorelbine	25	mg/m^2	2	
	Cisplatin +	75	mg/m^2	1	3 (adj)
	Docetaxel	75	mg/m^2	1	
	Carboplatin +	5	mg/mL/min	1	4 (neoadj) 3 (adj)
	Gemcitabine	1250	mg/m^2	2	
	Carboplatin +	5	mg/mL/min	1	3 (adj)
	Vinorelbine	25	mg/m^2	2	
	Carboplatin +	5	mg/mL/min	1	3 (adj)
	Docetaxel	75	mg/m^2	1	

Abbreviations: adj, adjuvant; CRT, chemoradiotherapy; EF, event-free; neoadj, m, minute; mg, milligram; mL, millilitre; neoadjuvant; PDC, platinum doublet chemotherapy.

[a] Treatment cycle length is 21 days for all treatments with a chemotherapy. For adjuvant monotherapy with durvalumab, the treatment cycle is 28 days.

[b] PDC can be administered either as neoadjuvant or adjuvant treatment. It may accompany IO or be administered on its own.

B 25. The costs of surgery were estimated as a weighted average of costs according to surgery type (thoracotomy or minimally invasive surgery). The proportion of patients undergoing a thoracotomy versus minimally invasive surgery for perioperative durvalumab and neoadjuvant PDC was informed by AEGEAN, with the proportions per surgery type for patients receiving neoadjuvant nivolumab +PDC assumed to be the same as for perioperative durvalumab.

a) Please discuss the plausibility of a higher proportion of thoracotomy for neoadjuvant PDC in UK clinical practice, as compared to perioperative durvalumab +PDC.

Response

The proportion of patients undergoing each type of surgery was informed by the AEGEAN trial, which was deemed to be the most robust evidence source due to the paucity of data justifying the proportion of surgery type following neoadjuvant treatment in this patient population in UK clinical practice.[18] The higher proportion of patients undergoing minimally invasive surgery in the perioperative durvalumab arm in comparison to neoadjuvant PDC aligns with TA876, [30] indicating a similar trend following neoadjuvant nivolumab + PDC versus neoadjuvant PDC.

b) Please provide justification for assuming the proportion of patients receiving thoracotomy to be the same for neoadjuvant nivolumab + PDC and perioperative durvalumab.

Response

The choice of surgery is multifactorial, but the proportion of patients receiving thoracotomy was not expected to be directly impacted by whether a patient received nivolumab + PDC or perioperative durvalumab.

c) The percentage of patients undergoing surgery, and the proportion assigned to each surgery type, differs substantially between the CS and TA876. Please provide a full overview of these differences, accompanied by justification as to the plausibility of these deviations.

Response

To say there are substantial differences between the CS and TA876's is debatable.[30]

- Across both trials and arms, the proportion of patients undergoing surgery are consistent (see table below).
- A higher proportion of IO-treated patients in both trials received minimally invasive surgery.
- The varying proportions assigned to each surgery type across the 2 trials may be attributed to a small percentage undergoing minimally invasive to thoracotomy in both arms in CM816, potentially balancing the categories if included in the minimally invasive group.

Table 36. Proportion of patients undergoing different surgery types in CM816 and AEGEAN

	Neoadjuvant nivolumab + PDC (CM816)		Perioperative durvalumab (AEGEAN)	
	Nivo + PDC (n = 179)	PDC (n = 179)	Durva + PDC (n = 366)	PDC (n= 374)
Patients with definitive surgery	83%	75%	81%	81%
Thoracotomy	59%	63%	50%	52%
Minimally invasive	30%	22%	50%	48%
Minimally invasive to thoracotomy	11%	16%	0%	0%

Abbreviations: PDC, platinum-doublet chemotherapy

d) Please provide an updated economic model and scenario analyses informing the proportion of patients receiving surgery (and distribution of surgery type) from TA876. For the perioperative durvalumab +PDC arm, assume the same proportions as for the neoadjuvant nivolumab +PDC arm.

Response

The economic model has been updated with an additional scenario analysis in which the proportion of patients receiving surgery (and surgery type) is sourced from TA876.[30] The updated results are presented in the Clarification Appendix.

Validation

B 26. Priority question. An advisory board meeting is referenced throughout the CS (CS reference 22).

a) Please provide all available information related to the advisory board meeting, including meeting minutes, report, and presentation slides.

Response

An advisory board report including a comprehensive summary and analysis of discussions and recommendations made by the UK clinical experts has been provided to the EAG.[29]

b) Please provide further information for all other sources of expert opinion used in the CS.

Response

AstraZeneca organized one advisory board, as outlined in the response to question B26a). All other references to clinical experts were drawn from those engaged in previous NICE technology appraisals, including TA569, TA531. TA584, TA612, TA632, TA642, TA683, TA684, TA770, TA798, TA705, TA823, TA851, TA876, and TA761.[30,40,49,62-65,76-82]

B 27. Further external validation of modelled effectiveness would be desirable. Please assess the validity of model outcomes by comparing them with:

a) Evidence used to develop the economic model (e.g., the pivotal trial).

b) Evidence not used to develop the economic model (e.g., registry data).

Response to 27a-b

The modelled effectiveness was validated using external data from the NSCLC MACG meta-analysis during the UK advisory board,[83] and with clinical experts (i.e., for external validation).[29] In addition, the modelled data appropriately fits the AEGEAN Kaplan-Meier, which provides internal validity against the pivotal trial.

B 28. CS Table 29 provides a summary of previous NICE TAs. For all relevant NICE TAs focussed on similar, potentially relevant, diseases, please provide cross-validations and elaborate on the differences regarding:

a) Model structure and assumptions

b) Input parameters related to:

   i. **Clinical effectiveness**

   ii. **Health state utility values**

   iii. **Resource use and costs**

c) Estimated (disaggregated) outcomes per comparator/intervention

   i. **Life years**

   ii. **QALYs**

   iii. **Costs**

Response to B28 a-c

Previous HTA submissions were reviewed to compare model structures in cost-effectiveness analyses and to understand the appropriate model structure for the analysis of perioperative durvalumab in resectable NSCLC. Table 29 in the CS and Table 56 in Appendix G in more detail, provide an overview of the NICE appraisals that were reviewed across neoadjuvant and adjuvant oncology indications such as NSCLC, breast cancer, gastrointestinal cancer, and melanoma.

Table 29 of the CS presents an overview of the model types and comparators used in the TAs identified. For additional insights into the considerations made by the EAG, you can refer to the details presented in Appendix G.

Overall, these appraisals demonstrated that other submissions also used a Markov or semi-Markov state transition model structure with the number of health states varying from three to seven health states. The EAG determined that the use of most

of these model approaches was suitable and aligned with other economic models in those disease areas.

However, the EAG did not consider the model structure that allowed transitions into subsequent health states based on treatment rather than disease progression, such as in TA326[84] to be appropriate. Another criticism from the EAG included the lack of differentiation from the pre- and post-progression states for DM health state, as in TA851,[82] because it does not reflect clinical practice. These criticisms were considered in the development of our economic model, therefore the model includes transition probabilities based on event recurrence from EF health state into other health states, and also includes a nested partitioned approach to model pre- and post-progression DM separately, similar to TA761,[49] and TA823.[40]

These tables do not present an overview of the input parameters and disaggregated outcomes per comparators from the TAs identified. This information was at times redacted from the public documents and therefore, no inferences can be made on how these items differ.

B 29. The model was validated both internally, by the model developer, and externally, by a third party consultancy and through a clinical advisory board.

a) For technical validation by the model developer, the CS suggests that a checklist was utilised. Please provide a detailed description of the validity assessment performed as well as the results.

b) The model was also validated by a third-party health economics and outcomes research (HEOR) consultancy. This round of model validation assessed the model's conceptual validity, internal technical validity, and included extreme value testing analysis and directional input testing. Please provide a detailed description and results regarding the third party validation.

c) Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

Response B29 a-c

The economic model has been validated by the model developer and a third-party HEOR consultancy. The Quality Control project took on four distinct phases:

- Model Inputs (bottom up) - A cell-by-cell verification user editable parameters in the model, as well as all parameters on the settings screen.
- TECH-VER checklist - The TECH-VER checklist is a comprehensive checklist for the technical verification of decision analytical models, aiming to help identify model implementation errors and their root causes while improving the transparency and efficiency of the verification efforts (Büyükkaramikli et al., 2019).[85]
- Comments on the overall model architecture.
- Additional quality checks - These include validating the use of best evidence, cross-validating against other published evidence, parameter and replication-based checks, and assessing the Macro/VBA in the model.

The results from both the internal and external validation exercises have been consolidated into a single section. The technical validation proposed some clarification regarding labelling, formatting and instructions. A few technical issues were identified such as, applying the incorrect utility for DM1 versus DM2, inconsistent using in SUMIF functions in the Traces (rows 10-11). All technical issues identified from the QC have been addressed in the economic model. The results of the TECH-VER checklist are presented below.

Table 37. Costs

#	Test description	Expected outcome	Result
3.1.1	Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes	Yes
3.1.2	Does the drug acquisition cost increase for higher weight or body surface area?	Yes	Yes
3.1.3	Set all costs to 0	No costs will be accumulated in the model at any time	Total costs become 0 for all states
3.1.4	Increase the treatment acquisition cost	Total cost and ICERs should increase	Yes
3.1.5	Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	Check the incremental cost results. Are they in line with the treatment costs?	Incremental LYs and QALYs match clinical effectiveness
3.1.6	Divide total undiscounted treatment acquisition costs by the average duration on treatment	This should be similar to treatment-related unit acquisition costs	There is a discrepancy of around £1000

Table 38. Utilities

#	Test description	Expected outcome	Result
3.2.1	Set all utilities to 1	The QALYs accumulated at a given time would be the same as the life years accumulated at that time	Yes
3.2.2	Set all utilities to 0	No QALYs will be accumulated in the model	Yes
3.2.3	Decrease all state utilities simultaneously	Lower QALYS will be accumulated each time	Yes

Table 39. Survival Curves

#	Test Description	Expected Outcome	Result
3.3.1	Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	Yes	Yes
3.3.2	In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?	No	No, the survival curves do not overlap
3.3.3	If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes	Yes, the Weibull distributions can generate values obtained from the Exponential and Gamma. The Generalised Gamma can generate values from the Gamma and Weibull
3.3.4	Is the HR calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	No, unless the treatment effect that is applied to the extrapolation comes from the same survival regression in which the extrapolation parameters are estimated	Treatment effect applied is assumed to be from same regression

Table 40. Transition Matrix

#	Test description	Expected outcome	Result
3.4.1	Check if the time conversions for probabilities were conducted correctly.	Yes	Partial

Table 41. Trace Sheets

#	Test description	Expected outcome	Result
3.5.1	Calculate the sum of the number of patients at each health state	Yes	All trace rows appropriately sum to 1
3.5.2	Check if all probabilities and number of patients in a state are greater than or equal to 0	Yes	Yes
3.5.3	Check if all probabilities are smaller than or equal to 1	Yes	Yes
3.5.4	Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	The total number of dead patients at a given period should be equal to or greater than the number of dead patients at any previous period	Yes, this cumulates correctly
3.5.5	In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes	No
3.5.6	Put mortality rates to 0	Patients never die, LYs equal to time horizon	No
3.5.7	Put mortality rate at extremely high	Patients die in the first few cycles	Yes
3.5.8	Set discount rates to 0	Discounted equal to undiscounted	Yes
3.5.9	Set discount rates to a higher value	Total discounted results should decrease	Yes
3.5.10	Set discount rates of costs/effects to an extremely high value	Total discounted results should be more or less the same as the discounted results accrued in the first cycles	Yes

Table 42. Results

#	Test description	Expected outcome	Result
3.6.1	Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	Same life-years and QALYs should be accumulated for all treatment at any time	No
3.6.2	In addition to the inputs above, set cost-related model inputs for all treatment options equal	Same costs, life-years, and QALYs should be accumulated for all treatment at any time	No
3.6.3	Total life years greater than the total QALYs	Yes	Yes
3.6.4	Undiscounted results greater than the discounted results	Yes	Yes
3.6.5	Divide undiscounted total QALYs by undiscounted life years	This value should be within the outer ranges (maximum and minimum) of all the utility value inputs	Yes, around 0.79 for both
3.6.6	Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Yes	Yes
3.6.7	If disentangled results are presented, do they sum up to the total results (e.g., different cost types sum up to the total costs estimate)?	Yes	Yes
3.6.8	Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements)	Zero cost and QALYs from AEs	Yes

Table 43. Uncertainty Analysis

#	Test description	Expected outcome	Result
3.7.1	Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Yes	Yes
3.7.2	Are the resulting ICER, incremental costs/QALYs with	Yes	Yes

	upper and lower bound of a parameter plausible and in line with a priori expectations?		
3.7.3	Check that all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e., upper bound≥mean≥lower bound)	Yes	No
3.7.4	Standard error and not standard deviation used in sampling	Yes	Yes
3.7.5	Lognormal/gamma distribution for HRs and costs/resource use	Yes	Yes
3.7.6	Beta for utilities and proportions/probabilities	Yes	Yes
3.7.7	Dirichlet for multinomial	Yes	Yes
3.7.8	Multivariate normal for correlated inputs (e.g., survival curve or regression parameters)	Yes	Yes
3.7.9	Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes	Yes
3.7.10	Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No	No, results are similar
3.7.11	If you take new PSA runs from the Microsoft Excel model, do you get similar results?	Yes	Yes, very similar results
3.7.12	Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes, although CE only has two
3.7.13	Does the PSA cloud demonstrate an unexpected behaviour or have an unusual shape?	No	No
3.7.15	Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes
3.7.16	Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always	Yes	Yes, mix around base case

	looking at more optimistic scenarios)?		
3.7.17	Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes
3.7.18	Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	Very high correlation
3.7.19	Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Yes	Yes

Table 44. Overall Validation/ Other Supplementary Checks

#	Target	Check	Result
3.8.1	Model costs	Visual inspection of appendix trace sheet through scrutinising the formulae in the trace sheets cell by cell	SUMIF formula inconsistency with < and <=, no errors otherwise
3.8.2	QALY	Visual inspection of appendix trace sheet through scrutinising the formulae in the trace sheets cell by cell	Incorrect utility value used for states "PF with DM" and "PD with DM" in the sheet "Trace - Durvalumab". AE disutility calculated incorrectly as the duration of Adverse Event effects is divided by the number of days in a week when the rest of the calculations suggest it should be divided by the number of days in a cycle.
3.8.3	LY	Visual inspection of appendix trace sheet through scrutinising the formulae in the trace sheets cell by cell	SUMIF formula inconsistency with < and <=, no errors otherwise

Severity and uncertainty

B 30. No severity calculation was included in the CS. To assess disease severity, please provide calculations of the absolute and proportional quality-adjusted life year (QALY) shortfall in line with the methodology outlines in the NICE Manual for Health Technology Evaluations.

Response

Using the Hernandez Alava et al. QALY shortfall calculator, the absolute and proportional QAY shortfall are presented below (Table 45).

Summary features of the QALY shortfall analysis:

- % female in the patient population: 28%
- Age of the patient population: 64

Table 45. QALY shortfall analysis results

Comparator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
Neoadjuvant PDC	11.24	5.90	Absolute:**5.34** Proportional: **47.53%**
Neoadjuvant nivolumab	11.24	6.93	Absolute: **4.31** Proportional: **38.37%**

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

B 31. Whist sensitivity and scenario analyses are included in Section CS B.3.9, no uncertainty section is included in the CS. Please provide the uncertainty section pertaining to the key areas of uncertainty throughout the submission.

Response

As stated in the CS, one uncertainty in assessing this technology is the absence of long-term EFS and OS data beyond the trial's follow-up period, however this uncertainty has been addressed by exploring various methods to extrapolate EFS beyond the trial duration. EFS measures disease progression that prevents surgery, recurrence, or death, reflecting treatment success across neoadjuvant and adjuvant

periods without being influenced by subsequent therapies. It aligns with treatment goals and can potentially serve as a surrogate for OS. Research demonstrates a strong association between EFS and OS, indicating their correlation and the impact of recurrence on OS neoadjuvant treatment.

Cost-effectiveness results

B 32. Priority question. A deterministic one-way sensitivity analysis (DOWSA) was conducted to identify key model drivers and examine key areas of uncertainty. However, many input parameters (e.g. treatment shares and distribution parameters to LRR and DM when patients experience an event) were excluded from the analysis. Please provide an updated economic model with the DOWSA conducted which includes all input parameters, with the exception of fixed unit prices and general population mortality.

Response

The economic model has been updated to include all input parameters that have been included in the PSA, in the DOWSA. These now include treatment shares and distribution parameters to LRR and DM, and total adverse events costs for the perioperative durvalumab arm. The “Parameters” sheet of the model has been amended to include the lower and upper bound values of the newly added DOWSA input parameters.

To avoid double-counting, only total costs (and not the separate components of these) for treatment monitoring, disease management and adverse events are included in the DOWSA. In addition, treatment acquisition costs per cycle are not included in the DOWSA and have been removed from the PSA for the same reason (double-counting); the individual components such as treatment shares and treatment durations are included in the DOWSA and PSA and unit prices are fixed.

B 33. Priority question. CS Appendix Table 80 provides a summary of health state costs for each considered treatment. Please provide the same table with treatment acquisition costs excluded.

Response

CS Appendix Table 80 has been updated to exclude treatment acquisition costs. The table can be found in the Clarification Appendix.

B 34. Priority question. Cost-effectiveness results currently include pairwise comparisons of perioperative durvalumab to the relevant comparators. Please provide and updated economic model and present the results of a fully incremental analysis. Please provide this for base case and scenario analyses (both deterministic and probabilistic) as well cost-effectiveness acceptability curves (CEACs) including all comparators simultaneously.

Response

The CS and economic model have been updated to include the results of a fully incremental analysis for the probabilistic analysis. The fully incremental analysis results for the update base-case are presented in Table 46.

Table 46. Probabilistic results: full incremental analysis

Technologies	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,016
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,151
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,770
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

A CEAC including all comparators simultaneously has been added and is presented in Figure 9 of the Clarification Appendix. Scenario analyses were only conducted deterministically (rather than probabilistically), due to the extensive amount of time that would be required for running probabilistic scenario analyses for all model comparators.

Sensitivity and scenario analyses

B 35. Within the economic model, a random seed is included for the probabilistic sensitivity analyses (PSA). For reproducibility purposes, please provide an updated economic model containing a fixed seed within the PSA.

Response

In the economic model's "Parameters" sheet (Column U), the fixed seed is being stored. When pressing the button to run the PSA macro ("PSA" sheet), a pop-up message will appear asking the user whether they wish to use the set of random numbers (i.e., fixed seed that has been already stored) or whether to generate a new set of random numbers. In addition, in the "Parameters" sheet (Column U cells 7-9) there is a button which creates a new set of random numbers when pressed.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

February, 2024

File name	Version	Contains confidential information	Date
Clarification Appendix	V1.0	Yes	14 March 2024

B.1. Updated 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 B.2.

B.1.1 *Base-case incremental cost-effectiveness analysis deterministic results*

The deterministic base case results are presented in Table 1 to Table 4. Per NICE guidelines the results are presented as pairwise comparisons given that perioperative durvalumab is expected to replace the individual comparator therapies.

Table 5 presents the incremental deterministic net health benefit (NHB) per treatment versus perioperative durvalumab.[1]

Table 1. 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]	£4,709

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

Table 2. 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]	£19,897

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

Table 3. 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 4. 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]	£4,345

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

Table 5. 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]	1.34	1.47
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	0.00	0.25
Surgery alone	[redacted]	[redacted]	2.88	2.81
Adjuvant PDC	[redacted]	[redacted]	1.42	1.55

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

B.2. Exploring uncertainty

B.2.1.1 *Updated incremental cost-effectiveness analysis probabilistic results*

B.2.1.1.1 Updated PSA results

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 6 to Table 9. The NHB probabilistic results are presented in Table 10.

Table 6. 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]	£6,151

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

Table 7. 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]	£24,016

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

Table 8. 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 9. 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]	£5,770

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

Table 10. Net health benefit (probabilistic)

Perioperative durvalumab vs.	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Neoadjuvant PDC	[redacted]	[redacted]	1.14	1.31
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	-0.13	0.13
Surgery alone	[redacted]	[redacted]	2.69	2.65
Adjuvant PDC	[redacted]	[redacted]	1.24	1.41

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 1 to Figure 4 and Figure 5 to

Figure 8, respectively. Figure 9 presents the CEAC for perioperative durvalumab versus all comparators simultaneously.

Figure 1. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant PDC

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

Figure 2. Incremental cost effectiveness plane: perioperative durvalumab versus neoadjuvant nivolumab + PDC

Abbreviations: QALY, quality-adjusted life year

Figure 3. Incremental cost effectiveness plane: perioperative durvalumab versus surgery alone

Abbreviations: QALY, quality-adjusted life year

Figure 4. Incremental cost effectiveness plane: perioperative durvalumab versus adjuvant PDC

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

Figure 5. CEAC: perioperative durvalumab versus neoadjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy

Figure 6. CEAC: perioperative durvalumab versus neoadjuvant nivolumab + PDC

Abbreviations: PDC, platinum-doublet chemotherapy

Figure 7. CEAC: perioperative durvalumab versus surgery alone

Figure 8. CEAC: perioperative durvalumab versus adjuvant PDC

Abbreviations: PDC, platinum-doublet chemotherapy

Figure 9. CEAC: perioperative durvalumab versus all comparators

Abbreviations: PDC, platinum-doublet chemotherapy

B.2.1.1 *Updated Deterministic sensitivity analysis*

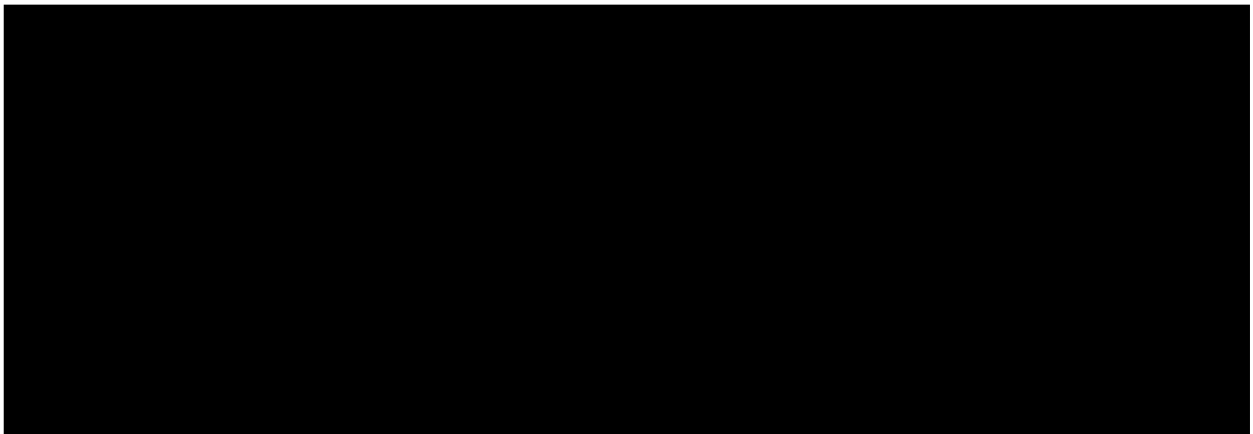
The results from the OWSA are presented in a tornado diagram for each pairwise comparison in Figure 10 to Figure 13. The tornado diagrams identify the top ten parameters which had the greatest impact on the ICER. In cases where a scenario led to any of the following outcomes: 'perioperative durvalumab dominated, 'perioperative durvalumab dominant,' or 'perioperative durvalumab is less costly and less effective,' the deterministic ICER is presented. This is to enable a clearer understanding of the impact of the other parameters.

Across all comparators, the key drivers of cost-effectiveness were the EFS HR versus neoadjuvant PDC, the discount rates for health benefits and costs, as well as the time period from last dose of neoadjuvant therapy to receiving adjuvant therapy. Additional information regarding the key parameters with the greatest impact and their estimated ICERs can be found in Appendix O.

Figure 10. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; PF with DM, Progression-free with distant metastasis (i.e. DM1); PD with DM, progressed disease with distant metastasis (i.e., DM2)

Figure 11. Tornado diagram from OWSA - perioperative durvalumab vs. neoadjuvant nivolumab + PDC



Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence PF with DM, Progression-free with distant metastasis (i.e. DM1); PD with DM, progressed disease with distant metastasis (i.e., DM2)

Figure 12. Tornado diagram from OWSA - perioperative durvalumab vs. surgery alone

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; PF with DM, Progression-free with distant metastasis (i.e. DM1); PD with DM, progressed disease with distant metastasis (i.e., DM2)

Figure 13. Tornado diagram from OWSA - perioperative durvalumab vs. adjuvant PDC

Abbreviations: DM, distant metastasis; EFS, event-free survival; LRR, locoregional recurrence; PF with DM, Progression-free with distant metastasis (i.e. DM1); PD with DM, progressed disease with distant metastasis (i.e., DM2)

B.2.1.2 *Updated Scenario analysis*

Table 11 presents an overview and justification for each scenario. Table 12 to Table 15 present the scenario analyses results for each comparator.

For the majority of the scenarios the results remained within or below the £20,000 - £30,000 per QALY range.

Table 11. Scenario analyses overview

Scenario nr.	Scenario	Base case parameter	Scenario parameter	Justification
1	Apply a warm-up period of 24 months starting from year 5	0	24	To assess the impact of using a warm-up period as per NICE TA876 base-case [2]
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	40.0%	[redacted]	Testing the impact of applying site of recurrence data from AEGEAN, pooled data across arms
3	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
4	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
5	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[2]
6	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
7	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)**
8	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 As requested by NICE in the clarification questions letter (Question B.11b)**
9	No IO re-treatment permitted	6	481	Testing an extreme scenario whereby retreatment is not permitted.
10	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)**
11	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)**
12	EF utility capped at UK general population norm	0.838	0.829	EF utility from the AEGEAN EQ-5D utility analysis is slightly higher than that of the UK general population, so testing the impact of using the latter.
13	Mean EF utility from Andreas et al. 2018	AEGEAN	Andreas et al. 2018	Exploring the impact of using different EF utility value i.e., from Andreas et al. 2018 in line with TA761 (EF=0.72)[3,4]
14	Discounting costs/effects: 1.5%	3.5%	1.5%	Exploring the impact of a lower discount rate for cost or health effects (extreme scenario)
15	Vial sharing	No	Yes	Testing the impact of allowing for vial sharing – **As requested by NICE in the clarification questions letter (Question B.23)**

Scenario nr.	Scenario	Base case parameter	Scenario parameter	Justification
16	IO in DM1: 65.3% based on IO restrictions from EF and LRR health states	80.0%	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)**
17	Health state utility values from TA823	EF: [redacted] LRR: [redacted] DM1: 0.759 DM2: 0.662	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[5] - **s requested by NICE in the clarification questions letter (Question B.16f)**
18	Health state utility values from TA761	EF: [redacted] LRR: [redacted] DM1: 0.759 DM2: 0.662	EF (DFS in TA761): [redacted] LRR: [redacted] DM1: [redacted] DM2: 0.640	Exploring the impact of using different utility values i.e., from TA761[4] - **As requested by NICE in the clarification questions letter (Question B.16b) [a]**
19	Type of surgery distribution based on TA876[2] - 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)[2] - **As requested by NICE in the clarification questions letter (Question B.25b)**

Abbreviations: CRT, chemoradiotherapy; 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

[a] DFS, LRR and DM1 values have been redacted from the CS but AstraZeneca has access internally

Table 12. Scenario analyses results perioperative durvalumab versus neoadjuvant PDC

Scenario nr.	Scenario label	Perioperative durvalumab vs. neoadjuvant PDC			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
N/A	Base case	[redacted]	[redacted]	£4,709	-
1	Apply a warm-up period of 24 months starting from year 5	[redacted]	[redacted]	£4,100	-12.9%
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	£5,528	17.4%
3	EFS distribution for neoadjuvant PDC arm: log-logistic	[redacted]	[redacted]	£3,709	-21.3%
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	£4,779	1.5%
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	£2,719	-42.3%
6	EFS HR: applied to standard extrapolations (lognormal)	[redacted]	[redacted]	£2,351	-50.1%
7	EFS HR: applied to standard extrapolations (exponential)	[redacted]	[redacted]	£3,913	-16.9%
8	EFS HR: applied to standard extrapolations (generalized gamma)	[redacted]	[redacted]	£2,751	-41.6%
9	No IO re-treatment permitted	[redacted]	[redacted]	£3,802	-19.3%
10	Waiting period before IO retreatment: 12 months	[redacted]	[redacted]	£4,365	-7.3%
11	All eligible for IO patients receive IO retreatment post-recurrence (i.e., same distribution in all arms, as of no IO comparators)	[redacted]	[redacted]	£9,038	91.9%
12	EF utility capped at UK general population norm	[redacted]	[redacted]	£4,781	1.5%
13	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	£5,857	24.4%
14	Discounting costs/effects: 1.5%	[redacted]	[redacted]	£2,260	-52.0%
15	Vial sharing	[redacted]	[redacted]	£4,681	-0.6%
16	IO in DM1: 65.3% based on IO restrictions from EF and LRR health states	[redacted]	[redacted]	£6,713	42.5%
17	Health state utility values from TA823	[redacted]	[redacted]	£4,953	5.2%
18	Health state utility values from TA761	[redacted]	[redacted]	£4,850	3.0%

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 13. 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]	£19,897	-
1	Apply a warm-up period of 24 months starting from year 5	[redacted]	[redacted]	£19,146	-3.8%
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	£20,017	0.6%
3	EFS distribution for neoadjuvant PDC arm: log-logistic	[redacted]	[redacted]	£18,046	-9.3%
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	£17,145	-13.8%
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	£15,018	-24.5%
6	EFS HR: applied to standard extrapolations (lognormal)	[redacted]	[redacted]	£9,908	-50.2%
7	EFS HR: applied to standard extrapolations (exponential)	[redacted]	[redacted]	£10,306	-48.2%
8	EFS HR: applied to standard extrapolations (generalized gamma)	[redacted]	[redacted]	£12,397	-37.7%
9	No IO re-treatment permitted	[redacted]	[redacted]	£28,468	43.1%
10	Waiting period before IO retreatment: 12 months	[redacted]	[redacted]	£23,261	16.9%
11	All eligible for IO patients receive IO retreatment post-recurrence (i.e., same distribution in all arms, as of no IO comparators)	[redacted]	[redacted]	£22,834	14.8%
12	EF utility capped at UK general population norm	[redacted]	[redacted]	£20,188	1.5%
13	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	£24,541	23.3%
14	Discounting costs/effects: 1.5%	[redacted]	[redacted]	£14,700	-26.1%
15	Vial sharing	[redacted]	[redacted]	£19,776	-0.6%
16	IO in DM1: 65.3% based on IO restrictions from EF and LRR health states	[redacted]	[redacted]	£21,240	6.7%
17	Health state utility values from TA823	[redacted]	[redacted]	£20,928	5.2%
18	Health state utility values from TA761	[redacted]	[redacted]	£20,447	2.8%
19	Type of surgery distribution based on TA876 - perioperative durvalumab same as neoadjuvant nivolumab + PDC	[redacted]	[redacted]	£20,169	1.4%

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 14. Scenario analyses results perioperative durvalumab versus surgery alone

Scenario nr.	Scenario label	Perioperative durvalumab vs. surgery alone			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
N/A	Base case	[redacted]	[redacted]	Dominant	-
1	Apply a warm-up period of 24 months starting from year 5	[redacted]	[redacted]	Dominant	-
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	Dominant	-
3	EFS distribution for neoadjuvant PDC arm: log-logistic	[redacted]	[redacted]	Dominant	-
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	Dominant	-
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	Dominant	-
6	EFS HR: applied to standard extrapolations (lognormal)	[redacted]	[redacted]	Dominant	-
7	EFS HR: applied to standard extrapolations (exponential)	[redacted]	[redacted]	£1,597	-
8	EFS HR: applied to standard extrapolations (generalized gamma)	[redacted]	[redacted]	Dominant	-
9	No IO re-treatment permitted	[redacted]	[redacted]	Dominant	-
10	Waiting period before IO retreatment: 12 months	[redacted]	[redacted]	Dominant	-
11	All eligible for IO patients receive IO retreatment post-recurrence (i.e., same distribution in all arms, as of no IO comparators)	[redacted]	[redacted]	£1,273	
12	EF utility capped at UK general population norm	[redacted]	[redacted]	Dominant	-
13	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	Dominant	-
14	Discounting costs/effects: 1.5%	[redacted]	[redacted]	Dominant	-
15	Vial sharing	[redacted]	[redacted]	Dominant	-
16	IO in DM1: 65.3% based on IO restrictions from EF and LRR health states	[redacted]	[redacted]	£262	-
17	Health state utility values from TA823	[redacted]	[redacted]	Dominant	-
18	Health state utility values TA761	[redacted]	[redacted]	Dominant	-

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 15. Scenario analyses results perioperative durvalumab versus adjuvant PDC

Scenario nr.	Scenario label	Perioperative durvalumab vs. adjuvant PDC			
		Incremental costs (£)	Incremental QALYs	ICER (Costs/QALY)	% Difference from base case ICER)
N/A	Base case	[redacted]	[redacted]	£4,345	-
1	Apply a warm-up period of 24 months starting from year 5	[redacted]	[redacted]	£3,766	-13.3%
2	Proportion of EFS non-death events being LRR using AEGEAN pooled across treatment arms data	[redacted]	[redacted]	£4,982	14.7%
3	EFS distribution for neoadjuvant PDC arm: log-logistic	[redacted]	[redacted]	£3,414	-21.4%
4	EFS distribution for neoadjuvant PDC arm: generalised gamma	[redacted]	[redacted]	£4,648	7.0%
5	EFS distribution for neoadjuvant PDC arm: Weibull	[redacted]	[redacted]	£2,579	-40.6%
6	EFS HR: applied to standard extrapolations (lognormal)	[redacted]	[redacted]	Dominant	-
7	EFS HR: applied to standard extrapolations (exponential)	[redacted]	[redacted]	£1,768	-59.3%
8	EFS HR: applied to standard extrapolations (generalized gamma)	[redacted]	[redacted]	Dominant	-
9	No IO re-treatment permitted	[redacted]	[redacted]	£3,465	-20.2%
10	Waiting period before IO retreatment: 12 months	[redacted]	[redacted]	£4,011	-7.7%
11	All eligible for IO patients receive IO retreatment post-recurrence (i.e., same distribution in all arms, as of no IO comparators)	[redacted]	[redacted]	£7,617	75.3%
12	EF utility capped at UK general population norm	[redacted]	[redacted]	£4,411	1.5%
13	Mean EF utility from Andreas et al. 2018	[redacted]	[redacted]	£5,402	24.3%
14	Discounting costs/effects: 1.5%	[redacted]	[redacted]	£2,113	-51.4%
15	Vial sharing	[redacted]	[redacted]	£4,126	-5.0%
16	IO in DM1: 65.3% based on IO restrictions from EF and LRR health states	[redacted]	[redacted]	£6,966	60.3%
17	Health state utility values from TA823	[redacted]	[redacted]	£4,570	5.2%
18	Health state utility values from TA761	[redacted]	[redacted]	£4,474	3.0%

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

B.3. Updated Appendices

Appendix J. Disaggregated results of the base-case incremental cost-effectiveness analysis

J.1 Base case population (MAIC-adjusted)

Table 16. Summary of QALY gain by health state per patient

Health state	QALYs				
	Perioperative durvalumab	Neoadjuvant PDC	Neoadjuvant nivolumab + PDC	Surgery alone	Adjuvant PDC
EF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LRR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; EF, event-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, locoregional recurrence; PDC, platinum-doublet chemotherapy; QALY, quality-adjusted life year.

Table 17. Summary of costs per health per patient

Health state	Costs (excluding treatment acquisition costs)				
	Perioperative durvalumab	Neoadjuvant PDC	Neoadjuvant nivolumab + PDC	Surgery alone	Adjuvant PDC
EF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LRR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (terminal care)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; EF, event-free; DM1, 1st line distant metastasis DM2, 2nd line distant metastasis; LRR, locoregional recurrence; PDC, platinum-doublet chemotherapy

Table 18. Summary of costs by item of resource use per patient

Health state	Costs				
	Perioperative durvalumab	Neoadjuvant PDC	Neoadjuvant nivolumab + PDC	Surgery alone	Adjuvant PDC
Treatment administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HCRU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment monitoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; HCRU, health care resource use

Table 19. Summary of proportion of patients alive

	Proportion of patients alive						
	Year 1	Year 2	Year 5	Year 10	Year 15	Year 20	Year 30
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PDC, platinum-doublet chemotherapy

Abbreviations: PDC, platinum-doublet chemotherapy

Appendix O. Deterministic sensitivity analysis

The 5 parameters which had the largest impact on the ICER, along with their estimated ICERs, are shown in Table 20 to Table 23.

Table 20. 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]	£1,623	£4,709	£69,736	£68,113
Discount rate - costs	0.02	0.04	0.06	£2,864	£4,709	£6,424	£3,561
Discount rate - health	0.02	0.04	0.06	£3,716	£4,709	£6,140	£2,424
Time from last dose of neoadjuvant to first dose of adjuvant treatment (months)	2.26	2.76	3.34	£4,709	£4,709	£2,999	£1,711
Utility - base	0.75	0.83	1.00	£4,238	£4,709	£5,677	£1,439

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

Table 21. 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]	-£137,777 [a]	£19,897	£2,043	£17,854
EFS: HR – Perioperative durvalumab vs. neoadjuvant PDC	[redacted]	[redacted]	[redacted]	£6,828	£19,897	-£33,910 [a]	£13,068
Discount rate - health	0.02	0.04	0.06	£15,726	£19,897	£25,892	£10,165
Utility - base	0.75	0.83	1.00	£17,907	£19,897	£23,987	£6,080
Time from last dose of neoadjuvant to first dose of adjuvant treatment (months)	2.26	2.76	3.34	£19,897	£19,897	£16,183	£3,713

[a] Durvalumab dominated

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

Table 22. 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]	£10,340	Dominated	-£5,452 [b]	£15,792
EFS: HR - Durvalumab vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£2,424 [b]	Dominated	£5,470	£7,894
PF with DM - Surgery alone arm: No treatment/BSC market share (No IO or retreatment)	0.16	0.23	0.29	-£3,586	Dominated	£359	£3,945
Discount rate - costs	0.02	0.04	0.06	-£3,322	Dominated	£5	£3,327
PF with DM - Surgery alone arm: Pembrolizumab market share (No IO or retreatment)	0.11	0.16	0.20	-£543	Dominated	-£2,814	£2,270

[b] Durvalumab dominant

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

Table 23. 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 - Neoadjuvant adjuvant PDC vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	-£116,873 [a]	£4,345	-£5,315 [b]	£111,558
EFS: HR - Perioperative durvalumab vs. Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	£1,442	£4,345	£55,910	£54,468
PF with DM - Adjuvant PDC arm: No treatment/BSC market share (No IO or retreatment)	0.16	0.23	0.29	£2,716	£4,345	£5,956	£3,241
Discount rate - costs	0.02	0.04	0.06	£2,678	£4,345	£5,898	£3,221
Discount rate - health	0.02	0.04	0.06	£3,430	£4,345	£5,664	£2,234

[a] Durvalumab dominated; [b] Durvalumab dominant

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

Appendix P. Alternative base-case results

P.1 Deterministic results

Deterministic results including total costs, life years gained (LYG), QALYs and incremental cost per QALY gained for perioperative durvalumab versus each comparator (except for neoadjuvant nivolumab + PDC, as discussed in Document B Section B.3.3.1.4) in the model are presented in Table 24 to Table 26, in the alternative base case. These results are based on the current commercial access agreement for durvalumab.

Table 24. 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]	£11,312

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

Table 25. Base-case probabilistic 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]	£157

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

Table 26. 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]	£10,425

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

B.4. References

1. York Health Economics Consortium. Net Health Benefit. http://www.yhec.co.uk/glossary/net-health-benefit/
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3. Andreas S, Chouaid C, Danson S, et al. Economic burden of resected (stage IB-IIIA) non-small cell lung cancer in France, Germany and the United Kingdom: A retrospective observational study (LuCaBIS). *Lung Cancer*. Oct 2018;124:298-309. doi:10.1016/j.lungcan.2018.06.007
4. 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;
5. 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

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project; £15,000 grant for Information Services; £165 Advisory Meeting Honorarium) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £480 Advisory board Honorarium) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Sanofi (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project) - Novocure (£30,000 for 1 year funding of GLCC project) - Roche (£30,000 for 1 year funding of GLCC project; £525 Speaker Fee, Lung Cancer Conference) - Regeneron (£30,000 for 1 year funding of GLCC project) - Merck (£30,000 for 1 year funding of GLCC project)

companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- AstraZeneca (£30,000 for 1 year funding of GLCC project; £19,500 for GLCC Project Translation; £300 for Advisory Board Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium) - Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker Fee) - Janssen (£24,000 grant funding for Ask The Nurse Service)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

to include in your submission?	

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	In patents with early stage lung cancer, who have a surgical resection of the tumour, with curative intent, the 5 year survival rates are reported to be up to 50%, with relapses in distant sites accounting for most failures. Relapse after surgery means that further potentially curative therapy is unlikely. Patients and their carers have continual anxiety that the lung cancer will come back. Symptoms of recurrent disease, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Historically, standard care for patients with resectable nsclc has been surgery. Sometimes, with the addition of chemotherapy after surgery (adjuvant) or chemoradiation before surgery (neoadjuvant). In March 2023, NICE TA 876 approved Nivolumab (a different immunotherapy), with chemotherapy, for the neoadjuvant treatment of resectable nsclc (NICE TA876). There is a need to explore additional therapies in improving outcomes and reducing recurrence in this patient group.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We note the study, published in NEJM in November 2023 (AEGEAN). In patients with resectable nsclc, perioperative Durvalumab plus neoadjuvant chemotherapy was associated with significantly greater event free survival and pathological complete response than neoadjuvant chemotherapy alone. Patient and carers would want the best outcome of chemoimmunotherapy. We are not aware of any direct comparisons, with other immunotherapies, in this indication.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy.
	It is important that, in administering neoadjuvant therapy, the window for successful surgery is not missed.
	Delays, whilst being assessed for and undergoing neoadjuvant treatment, have the potential for disease progression, making surgery not feasible. In this situation, patients could have been treated with up-front surgery (+/- adjuvant treatment) and potentially curative therapy, had neoadjuvant therapy not been undertaken.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	
14. Under current clinical practice do people have neo-adjuvant treatment, followed by surgery and then adjuvant treatment? If so, what treatments are used as neo-adjuvant and adjuvant therapies?	
14b. If the answer to Q14 is no, what do most people currently have as treatments around (before and/or after) their surgery for locally advanced NSCLC?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Neoadjuvant / adjuvant immunochemotherapy treatment is shown to be of benefit in the management of patients with early stage non small cell lung cancer • There is a need to develop therapy options to reduce the risk of recurrence after lung cancer surgery.

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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]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Contributions of authors

Mark Perry acted as joint project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence, critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, and contributed to the writing of the report. Bram Ramaekers and Willem Witlox acted as health economic project leads, critiqued the company's economic evaluation and contributed to the writing of the report. Bradley Sugden and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mubarak Patel acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Jiongyu Chen acted as a hybrid systematic reviewer/health economist, critiqued the clinical effectiveness methods/evidence and economic evaluation and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Robert Wolff acted as joint project lead, supervised meetings and the running of the project, and contributed to the writing of the report.

Abbreviations

2G	Second generation
3G	Third generation
AE	Adverse event
AACR	American Association for Cancer Research
AIC	Akaike Information Criteria
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BP	Blood pressure
BPI-SF	Brief Pain Inventory Short Form
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CD80	Cluster of differentiation 80
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
cm	Centimetres
COVID-19	Coronavirus disease 2019
CQ	Clarification question
CRD	Centre for Reviews and Dissemination
CrI	Credible Intervals
CRT	Chemoradiotherapy
CS	Company submission
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DFS	Disease-free survival
DIC	Deviance Information Criteria
DM	Distant metastases
DM1	distant metastases without further progression
DM2	Distant metastases with further progression
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
D120SU	Day 120 safety update
EAG	External Assessment Group
ECG	Electrocardiogram
ECM	Established clinical management
ECOG	Eastern Cooperative Oncology Group
EF	Event free
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
eMIT	Electronic market information tool
ELCC	European Lung Cancer Congress
EORTC	European Organisation for Research and Treatment of Cancer quality of life
EQ-5D	EuroQoL 5-Dimension
EQ-5D-5L	EuroQoL 5-Dimension, 5-Level health state utility index

ESMO	European Society for Medical Oncology
ESS	Effective sample size
EUR	Erasmus University Rotterdam
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-L	Functional Assessment of Cancer Therapy–Lung
FAD	Final Appraisal Document
FDA	Food and Drug Administration
FE	Fixing errors
FV	Fixing violations
HCRU	Healthcare resource utilisation
HEOR	Health Economics and Outcomes Research
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility values
HTA	Health Technology Assessment
HUI2/HUI3	Health Utility Index 2/3
IA	Interim analysis
IA1	Interim analysis 1
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
imAE	Immune-mediated adverse events
iNHB	Incremental net health benefit
IgG1κ	Immunoglobulin G1 kappa
IO	Immuno-oncology
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous(ly)
Kg	Kilograms
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LCL	Lower confidence limit
LCSS	Lung Cancer Symptom Scale
Ln	Natural logarithm (base e)
Logit	Natural logarithm of the odds ratio (i.e., LnOR)
LRR	Locoregional recurrence
LYG	Life years gained
M	Month
M^2	Square metres
MAIC	Matching adjusted indirect comparison
mITT	Modified intention-to-treat
MJ	Matters of judgement
MMRM	Mixed models for repeated measures
MPR	Major pathological response
MTP	Multiple Testing procedure
n	Number in sample
N	No
N0	No cancer cells in nearby nodes
N1	1-2 cancer cells in nearby nodes
N2	3-6 cancer cells in nearby nodes
N3	≥7 cancer cells in nearby nodes
NA	Not applicable
NACLC	North America Conference on Lung Cancer
NC	Not calculable
nCRT	Neoadjuvant chemoradiotherapy

NHB	Net health benefit
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NI	No information
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	Netherlands
(N)MA	(Network) meta-analysis
NMA	Network meta-analysis
NR	Not reached
NSCLC	Non-small-cell lung cancer
OR	Odds ratio
OS	Overall survival
ORR	Objective response rate
PAIC	Population-adjusted indirect comparison
pCR	Pathological complete response
PD	Progressed disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand-1
PD-L2	Programmed cell death ligand-2
PD-L1 TC ≥1%	Expression of PD-L1 on tumour membrane, at any intensity, in ≥1% of tumour cells
PDC	Platinum-doublet chemotherapy
PFS	Progression-free survival
PICOS	Population, Intervention, Comparator, Outcomes and Study Design
PN	Probably no
PORT	Post-operative radiation therapy
PRESS	Peer Review of Electronic Strategies
PPS	Post-progression survival
PrePS	Pre-progression survival
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcome
PS	Performance Status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
Q3W	Every 3 weeks
Q4W	Every 4 weeks
QLQ-C30	30-item Core Quality of Life Questionnaire
QLQ-LC13	13-item Lung Cancer Quality of Life Questionnaire
QTcF	QT interval (time from start of Q wave to end of the T wave) corrected for heart rate by Fridericia's cube root formula
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFS	Recurrence-free survival
RT	Radiotherapy
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-6D	Short-Form Six Dimensions
SLR	Systematic literature review
SoC	Standard of care

STC	Simulated treatment comparison
T1	Cancer contained within the lung
T2	Cancer between 3 cm and 5 cm across or with specific features
T3	Cancer between 5 cm and 7 cm or involving specific structures
T4	Cancer bigger than 7 cm or spread into other structures
TA	Technology Appraisal
TC	Tumour cells
TDT	Time to discontinuation of treatment
TKI	Tyrosine kinase inhibitor
TNM	Tumour-node-metastasis
TP	Transition probability
TRAEs	Treatment-related adverse events
TSD	Technical Support Document
TTO	Time-trade-off
TTP	Time to progression
Tx	Treatment
UCL	Upper confidence limit
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WCLC	World Conference on Lung Cancer
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
WTP	Willingness-to-pay

Table of Contents

Abbreviations **3**

Table of Tables **9**

Table of Figures **11**

1. Executive summary **12**

1.1 Overview of the EAG's key issues 12
1.2 Overview of key model outcomes 14
1.3 The decision problem: summary of the EAG's key issues 15
1.4 The clinical effectiveness evidence: summary of the EAG's key issues 16
1.5 The cost effectiveness evidence: summary of the EAG's key issues 21
1.6 Summary of the EAG's view 27

2. Critique of company's definition of decision problem **33**

2.1 Population 38
2.2 Intervention 38
2.3 Comparators 38
2.4 Outcomes 40
2.5 Other relevant factors 40

3. Clinical effectiveness **41**

3.1 Critique of the methods of review(s) 41
3.1.1 Searches 41
3.1.2 Inclusion criteria 43
3.1.3 Critique of data extraction 45
3.1.4 Quality assessment 45
3.1.5 Evidence synthesis 50
3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these) 50
3.2.1 Details of the included trials 50
3.2.2 Statistical analysis of the included trials 55
3.2.3 Baseline characteristics of the included trials 56
3.2.4 Risk of bias in the included trials 65
3.2.5 Efficacy results in the included trials 66
3.2.6 Adverse effects in the included trials 82
3.2.7 Ongoing studies 87
3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 88
3.3.1 MAIC 88
3.3.2 NMA 88
3.4 Critique of the indirect comparison and/or multiple treatment comparison 93
3.4.1 MAIC 93
3.4.2 NMA 99
3.5 Additional work on clinical effectiveness undertaken by the EAG 115
3.6 Conclusions of the clinical effectiveness section 116

4. Cost effectiveness **118**

4.1 EAG comment on company's review of cost effectiveness evidence 118
4.1.1 Searches performed for cost effectiveness section 118
4.1.2 Inclusion/exclusion criteria 120
4.1.3 Results of reviews performed for cost effectiveness section 122
4.2 Summary and critique of company's submitted economic evaluation by the EAG 122
4.2.1 NICE reference case checklist 122
4.2.2 Model structure 123
4.2.3 Population 126
4.2.4 Interventions and comparators 127
4.2.5 Perspective, time horizon and discounting 128
4.2.6 Treatment effectiveness and extrapolation 128
4.2.7 AEs 137
4.2.8 HRQoL 139
4.2.9 Resources and costs 142
4.2.10 Severity 151
4.2.11 Uncertainty 152

5. Cost effectiveness results 153

5.1 Company's cost effectiveness results 153
5.2 Company's sensitivity analyses 157
5.3 Model validation and face validity check 158
5.3.1 Face validity assessment 158
5.3.2 Technical verification 158
5.3.3 Comparisons with other TAs 159
5.3.4 Comparison with external data used to develop the economic model 159
5.3.5 Comparison with external data not used to develop the economic model 159

6. Evidence review group's additional analyses 161

6.1 Exploratory and sensitivity analyses undertaken by the EAG 161
6.1.1 EAG base-case 161
6.1.2 EAG exploratory scenario analyses 162
6.1.3 EAG subgroup analyses 162
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG 164
6.3 EAG's preferred assumptions 173
6.4 Conclusions of the cost effectiveness section 173

7. References 175

Table of Tables

Table 1.1: Summary of key issues 12
Table 1.2: Key issue 1: Omission of comparator of nCRT 15
Table 1.3: Key issue 2: Use of 'surgery alone' as proxy for 'active monitoring' 16
Table 1.4: Key issue 3: Omission of results for DFS 17
Table 1.5: Key issue 4: Use of safety DCO point for OS outcome only 17
Table 1.6: Key issue 5: No benefits in terms of QoL versus placebo 18
Table 1.7: Key issue 6: Lack of UK target population characteristics 18
Table 1.8: Key issue 7: Only outcome in ITC is EFS 19
Table 1.9: Key issue 8: Disjointed ITC analysis 19
Table 1.10: Key issue 9: No clear consistency evaluation in NMA 20
Table 1.11: Key issue 10: Piecewise approach may be less efficient than other methods 21
Table 1.12: Key issue 11: Cure assumption 21
Table 1.13: Key issue 12: Assumption that patients receiving BSC in the LRR health state cannot transit to the DM health state lacks face validity 22
Table 1.14: Key issue 13: State transition modelling approach 23
Table 1.15: Key issue 14: Estimation and assumptions regarding the EFS HRs 23
Table 1.16: Key issue 15: Estimation of transitions from the EFS health state 24
Table 1.17: Key issue 16: Relative effectiveness of IO retreatment 24
Table 1.18: Key issue 17: Estimation of the EF utility 25
Table 1.19: Key issue 18: Proportion of patients receiving IO treatment post-recurrence 25
Table 1.20: Key issue 19: Advisory Board summary report 26
Table 1.21: Key issue 20: Model validation 27
Table 1.22: Summary of EAG's preferred assumptions and ICER 29
Table 2.1: Statement of the decision problem (as presented by the company) 33
Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS) 41
Table 3.2: PICO eligibility criteria for the SLR 43
Table 3.3: Quality assessment results for included RCTs (York CRD checklist) 46
Table 3.4: Summary of AEGEAN methodology 51
Table 3.5: Key eligibility criteria for AEGEAN 54
Table 3.6: Study group definitions in AEGEAN 56
Table 3.7: Key patient demographics and baseline characteristics in AEGEAN 56
Table 3.8: Key disease characteristics in AEGEAN 57
Table 3.9: Baseline patient characteristics in AEGEAN, mITT population at EFS IA1, D120SU, and pCR IA1 59
Table 3.10: Baseline disease characteristics in AEGEAN, mITT population at EFS IA1, D120SU, and pCR IA1 61
Table 3.11: Quality assessment results for AEGEAN 65
Table 3.12: ORR prior to surgery (BICR RECIST v1.1), mITT population 71
Table 3.13: Compliance with EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L by visit 75
Table 3.14: EORTC QLQ-C30 global measure of health status/QoL 77
Table 3.15: EQ-5D-5L index and VAS scores change from baseline over time, with respect to neoadjuvant baseline (mITT) 78
Table 3.16: Summary of any grade AEs in AEGEAN in the overall study period, safety analysis set 83
Table 3.17: Summary of most common AEs in AEGEAN (overall study period), safety analysis set[a] 83

Table 3.18: Summary of AEs possibly related to surgery and surgical complications in AEGEAN (post-surgery period), underwent surgery, modified safety analysis set 84
Table 3.19: Summary of AEs possibly related to treatment or surgery at D120SU 85
Table 3.20: Summary of discontinuations at D120SU 86
Table 3.21: Overview of the mITT population NMA: sample size and number of events (overall and piecewise) 90
Table 3.22: Summary of population and treatment characteristics 91
Table 3.23: MAIC EFS HRs for perioperative durvalumab versus neoadjuvant nivolumab + PDC (unweighted and after weighting in the base-case and scenario 1) 94
Table 3.24: 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 1) 94
Table 3.25: MAIC sensitivity analysis EFS HRs for perioperative durvalumab versus neoadjuvant nivolumab + PDC (after weighting in the base-case and scenario 1 + inclusion of age and ECOG) ... 96
Table 3.26: MAIC piecewise EFS HRs (0-to-3-months and 3+ month time intervals) for perioperative durvalumab versus neoadjuvant nivolumab + PDC (after weighting in the base-case and scenario 1 + inclusion of age and ECOG) 96
Table 3.27: Baseline characteristics in CheckMate 816 and AEGEAN (unweighted and after weighting to match CheckMate 816 in the base-case and scenario 1 + inclusion of age and ECOG) 97
Table 3.28: ESS of AEGEAN (weighted to match CheckMate 816) in the base-case and scenario 1 . 98
Table 3.29: List of studies excluded from mITT population sensitivity analyses 100
Table 4.1: Data sources searched for economic evaluations (as reported in CS) 118
Table 4.2: Eligibility criteria for the SLRs 120
Table 4.3: NICE reference case checklist 122
Table 4.4: Key baseline patient and disease characteristics used in the economic model 126
Table 4.5: EFS piecewise (3 + months) HRs 131
Table 4.6: Distribution of treatments in the LRR and DM health states 134
Table 4.7: AE frequencies, costs, and disutilities 137
Table 4.8: HSUVs 140
Table 4.9: Overview of assumptions used to inform TDT in the neoadjuvant and adjuvant settings 143
Table 4.10: Distribution of PDC types per treatment arm 145
Table 4.11: Treatment costs per model cycle (monthly) 146
Table 4.12: Health state costs 148
Table 4.13: QALY shortfall analysis results 151

Table of Figures

Figure 3.1: KM plot of EFS, mITT population 67
Figure 3.2: pCR at final analysis, mITT population 69
Figure 3.3: MPR at final analysis, mITT population on 10 November 2022 70
Figure 3.4: Pathological regression, mITT population 71
Figure 3.5: KM plot of OS, mITT population at DCO 10 November 2022 73
Figure 3.6: KM of OS at D120SU 74
Figure 3.7: Subgroup analyses of EFS (BICR using RECIST 1.1), mITT population 79
Figure 3.8: Subgroup analysis of pCR, mITT population 81
Figure 3.9: Anchored PAIC diagram for AEGEAN versus CheckMate 816 93
Figure 3.10: Distribution of rescaled weights of AEGEAN (weighted to match CheckMate 816) in the base-case and scenario 1 98
Figure 3.11: Distribution network diagram of mITT AEGEAN versus adjuvant PDC and surgery alone, base-case 100
Figure 3.12: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (base-case) 103
Figure 3.13: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 1) 103
Figure 3.14: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 2) 104
Figure 3.15: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 3) 104
Figure 3.16: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 4) 105
Figure 3.17: Proportional hazards assessment for EFS in AEGEAN (mITT population) and CheckMate 816 from time = 0 months (i.e., full follow-up) 107
Figure 3.18: Proportional hazards assessment for EFS in AEGEAN (mITT population) and CheckMate 816 from time = 3 months (i.e., piecewise 3+ month interval) 108
Figure 3.19: Proportional hazards assessment for EFS in CHEST (mITT population) from time = 0 months and from time = 3 months 109
Figure 3.20: Proportional hazards assessment for EFS in Li et al. 2009 (mITT population) from time = 0 months and from time = 3 months 110
Figure 3.21: Proportional hazards assessment for EFS in MRC LU/22/NVALT 2/EORTC 09012 (mITT population) from time = 0 months and from time = 3 months 111
Figure 3.22: Proportional hazards assessment for EFS in NATCH (adjuvant PDC) (mITT population) from time = 0 months and from time = 3 months 112
Figure 3.23: Proportional hazards assessment for EFS in NATCH (surgery) (mITT population) from time = 0 months and from time = 3 months 113
Figure 3.24: Proportional hazards assessment for EFS in Rosell et al. 1994 (mITT population) from time = 0 months and from time = 3 months 114
Figure 3.25: Proportional hazards assessment for EFS in SWOG S9900 (mITT population) from time = 0 months and from time = 3 months 115
Figure 4.1: Model structure 124

1. Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 relates to the clinical effectiveness, and Section 1.5 is related to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report Sections
1	The omission of the comparator nCRT from the decision problem is based upon clinical opinion and not objective data.	2.3
2	Surgery alone is taken by the company to represent active monitoring, but the rationale is unclear. The EAG requires more information on the source of the company's clarification statement that surgery alone is the only relevant form of active monitoring for this population. Without details of the source of information, it is difficult to appraise the validity of the statement.	2.3
3	No results are provided for the DFS outcome, despite being reported by the CS to have been *"formally tested at the primary analysis of EFS (DCO 10 November 2022)"*.	3.2.5.2
4	For the OS outcome, data from the safety-analysis cut-off point at 120 days were also presented. This is the only clinical outcome where safety-analysis 120-day data were used.	3.2.5.5
5	HRQoL [redacted] between peri-operative durvalumab and placebo.	3.2.5.6
6	The sub-group analyses suggest there may be important effect modifiers. If the trial and UK target population differ in these characteristics, this may influence the generalisability of trial findings to the UK target population. However, there are no objective data provided on the characteristics of the UK target population, making it difficult to exclude population differences.	3.2.5.7
7	The only outcome to be subjected to ITC (MAIC or NMA) was EFS.	3.4
8	The AEGEAN trial is connected to all relevant comparators, as evidenced by the conduct of anchored ITCs with all comparators. However, the ITCs were separated into one for versus only neoadjuvant nivolumab and an NMA for adjuvant PDC and surgery alone.	3.4.2
9	In the NMA there is clinical heterogeneity across studies and between comparisons in terms of the treatments (i.e., 'neoadjuvant PDC' means different things in different papers) and populations, but no clear assessment of consistency.	3.4.2

ID1457	Summary of issue	Report Sections
10	A method of analysis that relaxes the proportional hazards assumption (i.e. using time-dependent HRs) might be more efficient than the piecewise method used.	3.4.2
11	The CS stated that *"the model assumes that 95% of patients would achieve cure if they have not experienced an EFS event at 5 years"*. Moreover, the CS assumes that cure involves maintaining an event-free status for patients until death. According to the company, this definition of cure was supported by the UK Advisory Board in January 2024. However, despite requested (CQ B26), the company did not provide further details related to this Advisory Board Meeting (only a concise summary, that was not reviewed by the consulted clinical advisors, was available to the EAG).	4.2.2
12	Assumption that patients receiving BSC in the LRR health state cannot transit to the DM health state lacks face validity	4.2.2
13	The CS stated that an *"assumption was made that those patients who received BSC in LRR" … "would transition to the death state directly (i.e., not transition to DM and receive further treatment)"*. In other words, patients receiving BSC in the LRR health state cannot transit to the DM health state.	4.2.2
14	The company adopted a state transition modelling approach, rather than the partitioned survival model that is also commonly used in oncology. State transition modelling allows using external sources of evidence and thus is not reliant on extrapolation of immature OS data. As stated in the CS, the use of state transition models may be deemed appropriate in cases where the cost effectiveness analysis requires a complex disease pathway to be analysed.	4.2.6
15	The company assumed constant EFS HRs based on two separate analyses (MAIC and NMA). It is unclear whether constant HRs are plausible, both over the observed data period as well as in the extrapolation of treatment effectiveness (i.e. whether treatment waning is applicable). No time-varying HR approach was explored by the company in response to CQs A24 and B9.	4.2.6
16	Transition probabilities originating from the EF state were calculated based on EFS from the AEGEAN trial. Subsequently, estimated EFS was used to calculate transition probabilities for: EF to LRR (TP1), EF to DM (TP2), and EF to death (TP3). Additional explanation was provided regarding the calculation of TP1-3 in response to CQ B10. The EAG believes the approach adopted by the company is in general reasonable. However, the probability of the event being LRR or DM was assumed to be constant over time as well as equal for all treatments (i.e. time and treatment independent). This is inconsistent with clinical expert opinion obtained by the EAG. Moreover, the company acknowledged (response to CQ B10f) the potential treatment dependency of LRR or DM probabilities.	4.2.6
17	HRQoL data collected in the AEGEAN trial were analysed using MMRM to estimate the EF health state utility in the economic model. The EAG's concerns relate to 1) the EF utility was informed by the neoadjuvant period of the AEGEAN trial only (i.e. data from the adjuvant period were not used), 2) the EF utility in the company's base-case was higher than the age-adjusted UK general population utility, and 3) missing HRQoL data in the AEGEAN trial.	4.2.8

ID1457	Summary of issue	Report Sections
18	In the LRR and DM health states, patients were deemed eligible for IO (re)treatment if they received IO treatment in the EF health state and did not progress within 6 months, or did not receive IO in EF, and had PD-L1 ≤1% (informed by AEGEAN). Of the eligible patients, 70% and 80% of patients were modelled to receive post-recurrence IO for LRR and DM without further progression (DM1), respectively. Based on clinical expert opinion, the EAG questions the appropriateness of using a 6-month progression cut-off to determine eligibility for post-recurrence IO, provided that this is the minimum threshold for funding by NHS England. Clinical experts in the company Advisory Board suggested 6-12 months with a 6 month cut-off being used for the primary analyses. Further, the EAG questions the proportions of eligible patients assumed to receive IO.	4.2.9
19	A summary report was provided for the AEGEAN Health Economic Advisory Board held on 19 January 2024. The company extensively refers to this report/the Advisory Board meeting. The document highlights that the summary report had not been reviewed by the participating clinical advisors. It was also clarified that a full meeting report is yet to be finalised and shared with clinical advisors for review and comment. The EAG has been unable to review the final summary report nor were further materials available (e.g. the meeting presentation slides).	5.3.1
20	Model validation. In response to CQ B27, no model comparisons between model outcomes were provided related to: evidence used to develop the economic model, and evidence not used to develop the economic model.	5.3.2

BSC = best supportive care; CQ = clarification question; CS = company submission; DCO = data cut-off; DFS = disease-free survival; DM = distant metastases; EAG = External Assessment Group; EF = event free; EFS = event-free survival; HR = hazard ratio; HRQoL = health-related quality of life; IO = immuno-oncology; ITC = indirect treatment comparison; LRR = locoregional recurrence; MAIC = matching adjusted indirect comparison; MMRM = mixed models for repeated measures; nCRT = neoadjuvant chemoradiotherapy; NHS = National Health Service; NMA = network meta-analysis; OS = overall survival; PDC = platinum-doublet chemotherapy; PD-L1 = programmed cell death ligand-1; TP = transition probability; UK = United Kingdom

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased event free (EF) health state occupancy for perioperative durvalumab + platinum-doublet chemotherapy (PDC). This resulted in a large pre-progression benefit, in terms of QALYs accrued, for perioperative durvalumab in the EF health state ([redacted]) compared to comparator QALYs accrued in the EF health state (ranging from [redacted] for surgery alone to [redacted] for neoadjuvant nivolumab + PDC).
- Increase overall survival (OS) for perioperative durvalumab + PDC, compared to comparators. The proportion of patients alive was higher for perioperative durvalumab + PDC at year 1 ([redacted]), year 2 ([redacted]), year 5 ([redacted]), year 10 ([redacted]), year 15 ([redacted]), year 20 ([redacted]), and year 30 ([redacted]), compared to all other comparators (CS Appendix J).

Overall, the technology is modelled to affect costs by:

- Higher treatment acquisition costs for perioperative durvalumab + PDC compared with comparators (difference ranging from [redacted] to [redacted]).
- Higher health state costs (healthcare resource utilisation (HCRU) and treatment monitoring) for comparators in post recurrence health states compared with perioperative durvalumab + PDC. Differences ranged from [redacted] to [redacted] for locoregional recurrence (LRR), [redacted] to [redacted] for distant measures 1 (DM1), and [redacted] to [redacted] for DM2.
- Higher treatment costs (administration costs and treatment acquisition costs) for comparators in post recurrence health states compared with perioperative durvalumab + PDC. Differences ranged from [redacted] to [redacted] for LRR, [redacted] to [redacted] for DM1, and [redacted] to [redacted] for DM2.

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

- Event-free survival (EFS) hazard ratios (HRs)
- Discount rates for costs and effects
- Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following CS scenarios that have a substantial impact on the ICER (in at least one of the comparisons):
- EFS HR: applied to standard extrapolations
- EFS distribution for neoadjuvant PDC arm: Weibull
- EFS distribution for neoadjuvant PDC arm: loglogistic
- Discounting costs/effects: 1.5%
- Mean EF utility from Andreas et al. 2018
- No immuno-oncology (IO) retreatment permitted

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the CS is broadly in line with the Final Scope issued by NICE. However, there were concerns about the omission of the key comparators neoadjuvant chemoradiotherapy (nCRT) (Table 1.2) and the use of 'surgery alone' as a proxy for 'active monitoring' (Table 1.3).

Table 1.2: Key issue 1: Omission of comparator of nCRT

Report Section	**2.3**
Description of issue and why the EAG has identified it as important	The omission of nCRT is made solely because of clinical opinion in the CS. The company makes it clear that nCRT is not often given in the scope population, which the EAG accepts. However, this cannot be automatically inferred to mean that nCRT is inferior to perioperative durvalumab in the scope population, and thus eligible for exclusion. Lack of use is also acknowledged in the NICE guideline NG122 and yet the guideline still recommends that it be considered, at least for some patients. The EAG considers that nCRT cannot be legitimately excluded as a comparator until it can be confirmed that: There is evidence from a direct comparison that nCRT is inferior to perioperative durvalumab in the scope population. Alternatively, if the other comparators are inferior to

Report Section	2.3
	perioperative durvalumab in the scope population, and nCRT is also inferior or equivalent to the other comparators in the scope population, then nCRT's inferiority to perioperative durvalumab could be indirectly inferred. Previous scientific appraisal of the efficacy of nCRT has not been carried out in the scope population. If these conditions cannot be shown to apply, then the possibility remains that nCRT may be more effective than perioperative durvalumab, in which case exclusion of nCRT as a comparator might lead to the spurious conclusion that perioperative durvalumab is the most effective treatment available.
What alternative approach has the EAG suggested?	A convincing rationale based on clinical evidence. If this is not possible, inclusion of nCRT.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	A convincing rationale based on clinical evidence. If this is not possible, inclusion of nCRT.
CS = company submission; EAG = External Assessment Group; nCRT = neoadjuvant chemoradiotherapy	

Table 1.3: Key issue 2: Use of 'surgery alone' as proxy for 'active monitoring'

Report Section	2.3
Description of issue and why the EAG has identified it as important	Surgery alone is taken by the company to represent active monitoring, but the rationale is unclear. The EAG require more information on the source of the company's clarification statement that surgery alone is the only relevant form of active monitoring for this population. Without details of the source of information, it is difficult to appraise the validity of the statement.
What alternative approach has the EAG suggested?	Information on the source of the company's clarification statement that surgery alone is the only relevant form of active monitoring for this population. If this source does not provide an adequate rationale, inclusion of studies where other forms of active monitoring are used.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Information on the source of the company's clarification statement that surgery alone is the only relevant form of active monitoring for this population. If this source does not provide an adequate rationale, inclusion of studies where other forms of active monitoring are used.
EAG = External Assessment Group	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified two major concerns with the evidence presented on the clinical effectiveness, namely omission of results for disease-free survival (DFS) (Table 1.4), use of the safety data cut-

off (DCO) for OS only (Table 1.5), the lack of any benefit in health-related quality of life (HRQoL) versus placebo (Table 1.6), lack of United Kingdom (UK) target population characteristics (Table 1.7), restriction of the indirect treatment comparison (ITC) to only one of the NICE Final Scope outcomes (Table 1.8), a disjointed ITC analysis (Table 1.9), no clear consistency evaluation in network meta-analysis (NMA) (Table 1.10), and the possibly inefficient use of a piecewise approach in the NMA (Table 1.11).

Table 1.4: Key issue 3: Omission of results for DFS

Report Section	**3.2.5.2**
Description of issue and why the EAG has identified it as important	No results are provided for the DFS outcome, despite being reported by the CS to have been "formally tested at the primary analysis of EFS (DCO 10 November 2022)". The EAG understands that, per the rigorous Multiple Testing Procedure, the first interim analysis with a statistical analysis for DFS would only occur when there were 400 patients with a minimum of 7 months follow-up. However, the EAG does not understand why the raw DFS data could not have been reported without statistical analysis by an independent unblinded team distinct from the blinded study team, given that DFS is an outcome decreed by NICE and therefore of relevance for the committee.
What alternative approach has the EAG suggested?	The raw DFS data could be reported without statistical analysis by an independent unblinded team distinct from the blinded study team.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	The raw DFS data could be reported without statistical analysis by an independent unblinded team distinct from the blinded study team.
CS = company submission; DCO = data cut-off; DFS = disease-free survival; EAG = External Assessment Group; EFS = event-free survival; NICE = National Institute for Clinical and Health Excellence	

Table 1.5: Key issue 4: Use of safety DCO point for OS outcome only

Report Section	**3.2.5.5**
Description of issue and why the EAG has identified it as important	For the OS outcome, which yielded a result suggesting the two arms were [redacted] on the 10 November 2022 DCO point, data from the safety-analysis cut-off point at 120 days were also presented. This is the only clinical outcome where safety-analysis 120-day data were used. The EAG acknowledges that this approach was agreed with the FDA, but also notes that the 120-day data were, like the 10 November 2022 data, informal data. This is because the MTP would also designate the 120-day OS analysis as informal (as DFS had not yet been declared statistically significant). If neither the 10 November 2022 nor 120-day OS data were 'formal' analyses, they appear to have equal status. Therefore, the EAG does not understand why the more conservative data yielded at the 10 November 2022 DCO were not used as the solely presented analysis, to remain in line with the other outcomes.

Report Section	3.2.5.5
What alternative approach has the EAG suggested?	Data from the 120-day DCO should not be reported and the OS data from the 10 November 2022 analysis should be presented alone.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Data from the 120-day DCO should not be reported and the OS data from the 10 November 2022 analysis should be presented alone.
DCO = data cut-off; DFS = disease-free survival; EAG = External Assessment Group; FDA = Food and Drug Administration; MTP = Multiple Testing procedure; OS = overall survival	

Table 1.6: Key issue 5: No benefits in terms of QoL versus placebo

Report Section	3.2.5.5
Description of issue and why the EAG has identified it as important	No benefits were observed for perioperative durvalumab versus placebo in terms of HRQoL. Since HRQoL is the most patient-centred outcome, this lack of benefit is of importance. Currently, the HRQoL data is not included in the ITC.
What alternative approach has the EAG suggested?	HRQoL data should be subjected to an ITC (alongside EFS) so that this outcome can be reflected in the health economic analysis.
What is the expected effect on the cost effectiveness estimates?	Likely to reduce it.
What additional evidence or analyses might help to resolve this key issue?	HRQoL data should be subjected to an ITC (alongside EFS) so that this outcome can be reflected in the health economic analysis.
EAG = External Assessment Group; EFS = event-free survival; HRQoL = health-related quality of life; ITC = indirect treatment comparison; QoL = quality of life	

Table 1.7: Key issue 6: Lack of UK target population characteristics

Report Section	3.2.5.7
Description of issue and why the EAG has identified it as important	The sub-group analyses suggest there may be important effect modifiers. For the outcome of EFS, the characteristics of gender and smoking status appear important effect modifiers. For the outcome of pCR, the characteristics of PD-L1 expression, lymph node station, disease stage, smoking status and geographic region appear potentially important. If the trial and UK target population differ in these characteristics, this may influence the generalisability of trial findings to the UK target population. However, there are no objective data provided on the characteristics of the UK target population, making it difficult to exclude population differences.
What alternative approach has the EAG suggested?	The company should provide UK target population characteristics, but if these are not available then the committee should adopt a conservative approach to the external validity of trial results.

Report Section	3.2.5.7
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	The company should provide UK target population characteristics, but if these are not available then the committee should adopt a conservative approach to the external validity of trial results.
EAG = External Assessment Group; EFS = event-free survival; pCR = pathological complete response; PD-L1 = programmed cell-death ligand 1; UK = United Kingdom	

Table 1.8: Key issue 7: Only outcome in ITC is EFS

Report Section	3.4.1
Description of issue and why the EAG has identified it as important	The only outcome to be subjected to ITC (MAIC or NMA) was EFS. The EAG would argue that outcomes other than EFS have been designated by NICE as relevant to the proper evaluation of the intervention against the designated comparators, and therefore these should have been appraised, as far as possible, in accompanying MAICs. One outcome cannot determine the superiority of one treatment over another, given that different outcomes respond differently, and therefore an appraisal of superiority utilising only one outcome is incomplete and invalid.
What alternative approach has the EAG suggested?	Inclusion of other key scope outcomes (i.e. HRQoL).
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Inclusion of other key scope outcomes.
EAG = External Assessment Group; EFS = event-free survival; HRQoL = health-related quality of life; ITC = indirect treatment comparison; MAIC = matching adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis	

Table 1.9: Key issue 8: Disjointed ITC analysis

Report Section	3.4.2
Description of issue and why the EAG has identified it as important	The AEGEAN trial is connected to all relevant comparators, as evidenced by the conduct of anchored ITCs with all comparators. However, the ITCs were separated into an MAIC for durvalumab and neoadjuvant nivolumab and a separate NMA for durvalumab, adjuvant PDC and surgery alone. 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. The lease biased estimates of all treatment effects would therefore

Report Section	3.4.2
	appear to be those estimated in the UK clinical practice population.
What alternative approach has the EAG suggested?	An all-encompassing NMA (that would cover all three decision problem comparators), using multilevel network meta-regression as recommended by Philippo et al. 2020.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Use of multi-level network meta-regression as mentioned by the company in Appendix D and recommended by Phillippo et al. 2020 might permit the estimation of treatment effects most consistent with UK clinical practice.
EAG = External Assessment Group; HR = hazard ratio; ITC = indirect treatment Comparison; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis; PDC = platinum-doublet chemotherapy; UK = United Kingdom	

Table 1.10: Key issue 9: No clear consistency evaluation in NMA

Report Section	3.4.2
Description of issue and why the EAG has identified it as important	In the NMA there is clinical heterogeneity across studies and between comparisons in terms of the treatments (i.e., 'neoadjuvant PDC' means different things in different papers) and populations. The sensitivity analyses put forward by the company appear insufficient to account for this. All the sensitivity analysis models have a better fit to the data than the base-case, as shown by their much lower DIC values but it is unclear how consistency models and inconsistency models compare to each other in terms of DIC for each scenario. The company claims that the closed loop in the NMA is formed solely by the multi-armed NATCH trial, which would make consistency testing impossible, but the EAG notes that the neoadjuvant PDC versus surgery comparison in the loop is contributed to by four trials additional to NATCH. The estimate for this arm will therefore not automatically be consistent with the other two arms (as it would have been had that arm been solely dependent on the NATCH data). Therefore, the consistency of this loop could and should have been estimated, by comparing DIC values for the consistency and inconsistency models.
What alternative approach has the EAG suggested?	Comparison of DIC for consistency and inconsistency models.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Comparison of DIC for consistency and inconsistency models.
DIC = Deviance Information Criterion; EAG = External Assessment Group; NMA = network meta-analysis; PDC = platinum-doublet chemotherapy	

Table 1.11: Key issue 10: Piecewise approach may be less efficient than other methods

Report Section	**3.4.2**
Description of issue and why the EAG has identified it as important	The MAIC and the NMA both employed a Cox proportional hazards model, although a piecewise analysis, splitting the analysis into the 0-3 and >3 months epoch, was used to try to avoid the problem of the overall dataset not following the proportional hazards assumption given the probable change in the HR between the 0-3 and >3 months periods observed in the AEGEAN trial. However, it appears that there was no consideration of non-proportional hazards after 3 months or between durvalumab and any of the comparators outside of the AEGEAN trial i.e. neoadjuvant nivolumab, surgery or adjuvant PDC.
What alternative approach has the EAG suggested?	A method of analysis that relaxes the proportional hazards assumption i.e. using time-dependent HRs would perhaps be more efficient.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	To conduct a NMA that employs a method allowing time-varying HRs such as that described by Cope et al. 2020, which was used in NICE TA865.
EAG = External Assessment Group; HR = hazard ratio; MAIC = matching adjusted indirect comparison; NICE = National Institute of Health and Care Excellence; NMA = network meta-analysis; PDC = platinum-doublet chemotherapy; TA = Technology Appraisal	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6.

The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

Table 1.12: Key issue 11: Cure assumption

Report Section	**4.2.2**
Description of issue and why the EAG has identified it as important	The CS stated that "*the model assumes that 95% of patients would achieve cure if they have not experienced an EFS event at 5 years*". Moreover, the CS assumes that cure involves maintaining an EFS for patients until death. According to the company, this definition of cure was supported by the UK Advisory Board in January 2024. However, despite requested (CQ B26), the company did not provide further details related to this Advisory Board Meeting (only a concise summary, that was not reviewed by the consulted clinical advisors, was available to the EAG). Moreover, according to the company's response to CQ B7, the total proportion of patients assumed to be cured (based on the above-mentioned definition) was [redacted] for patients that received perioperative durvalumab, neoadjuvant PDC, neoadjuvant nivolumab + PDC, adjuvant PDC and surgery alone respectively.

Report Section	4.2.2
	Given the lacking empirical evidence and details of the UK Advisory Board, it was unclear whether these proportions as well as the cure definition are plausible. Given the uncertainty regarding cure, the EAG considers both the company's cure assumption as well as no cure assumption as potentially plausible scenarios.
What alternative approach has the EAG suggested?	It would be informative if the company would conduct the scenario analyses requested in CQ B7 (assuming alternative cure definitions), to explore the impact of this uncertainty.
What is the expected effect on the cost effectiveness estimates?	Alternative assumptions regarding cure can potentially increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	See above and potentially provide analyses based on more mature data than the current DCO (10 November 2022), if available.
CQ = clarification question; CS = company submission; DCO = data cut-off; EAG = External Assessment Group; EFS = event-free survival; ICER = incremental cost-effectiveness ratio; PDC = platinum-doublet chemotherapy; UK = United Kingdom	

Table 1.13: Key issue 12: Assumption that patients receiving BSC in the LRR health state cannot transit to the DM health state lacks face validity

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	The CS stated that an "*assumption was made that those patients who received BSC in LRR*" … "*would transition to the death state directly (i.e., not transition to DM and receive further treatment)*". In other words, patients receiving BSC in the LRR health state cannot transit to the DM health state. The clinical expert opinion obtained by the EAG stated that "*it is too strong to say that patients receiving BSC could not transit to DM health state and only to death health state. Some patients may transit to the death health state after locoregional recurrence but many would develop metastatic disease and eventually succumb to their disease due to this*".
What alternative approach has the EAG suggested?	Perform the scenario analyses requested in CQ B4, to explore the impact of this simplifying assumption.
What is the expected effect on the cost effectiveness estimates?	Alternative assumptions can potentially increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	See above.
CQ = clarification question; CS = company submission; BSC = best supportive care; DM = distant metastases; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence	

Table 1.14: Key issue 13: State transition modelling approach

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	The company adopted a state transition modelling approach, rather than the partitioned survival model that is also commonly used in oncology. State transition modelling allows using external sources of evidence and thus is not reliant on extrapolation of immature OS data. As stated in the CS, the use of state transition models may be deemed appropriate in cases where the cost effectiveness analysis requires a complex disease pathway to be analysed. The state transition model might be implemented sub-optimally. Particularly given that time-dependent transition probabilities (TP4-6 in CS Figure 20) are estimated for the LRR and DM health states, i.e. to estimate the long-term costs and consequences. These parametric survival models are estimated based on external sources of evidence, with transition probabilities as a function of the model cycle time (i.e. time dependent treatment probabilities). However, patients enter the LRR and DM health states at different points in time. Hence, the transition probabilities should be implemented as a function of the time since entry into the LRR or DM health state rather than as a function of the model cycle time. This erroneous implementation of time dependent transition probabilities might bias the estimated cost and consequences.
What alternative approach has the EAG suggested?	As specified in CQ B6, there are multiple potential solutions to overcome the discrepancy described above regarding transition probabilities as a function of the model cycle time versus transition probabilities as a function of the time since entry into the LRR or DM health state. This includes the use of transition probabilities that are constant over time, the inclusion of tunnel states and the use of patient-level simulation.
What is the expected effect on the cost effectiveness estimates?	In CQ B6 the company is asked to elaborate on the implications of this erroneous implementation of time dependent transition probabilities mentioned above and report on the potential impact on the estimated costs and consequences using scenario analysis. Unfortunately, this was not addressed by the company. As a result, it is unclear to what degree the time-dependent transition probabilities for TP4-6 do bias the estimated outcomes.
What additional evidence or analyses might help to resolve this key issue?	Elaborate on the implications of the erroneous implementation of time dependent transition probabilities mentioned above and report on the potential impact on the estimated costs and consequences using scenario analysis.
CS = company submission; DM = distant metastases; EAG = External Assessment Group; LRR = locoregional recurrence; OS = overall survival; TP = transition probability	

Table 1.15: Key issue 14: Estimation and assumptions regarding the EFS HRs

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The company assumed constant EFS HRs based on two separate analyses (MAIC and NMA). It is unclear whether constant HRs are plausible, both over the observed data period as well as in the extrapolation of treatment effectiveness (i.e. whether treatment waning is applicable). No time-varying HR approach was explored by the company in response to CQs A24 and B9.

Report Section	4.2.6
What alternative approach has the EAG suggested?	Provide i) the time-varying HR approach mentioned in CQs A24 and B9 and ii) explore the impact of treatment waning (see CQ B9e).
What is the expected effect on the cost effectiveness estimates?	Alternative assumptions can potentially increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	See above.
EAG = External Assessment Group; EFS = event-free survival; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis	

Table 1.16: Key issue 15: Estimation of transitions from the EFS health state

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Transition probabilities originating from the EF state were calculated based on EFS from the AEGEAN trial. Subsequently, estimated EFS was used to calculate transition probabilities for: EF to LRR (TP1), EF to DM (TP2), and EF to death (TP3). Additional explanation was provided regarding the calculation of TP1-3 in response to CQ B10. The EAG believes the approach adopted by the company is in general reasonable. However, the probability of the event being LRR or DM was assumed to be constant over time as well as equal for all treatments (i.e. time and treatment independent). This is inconsistent with clinical expert opinion obtained by the EAG. Moreover, the company acknowledged (response to CQ B10f) the potential treatment dependency of LRR or DM probabilities.
What alternative approach has the EAG suggested?	Provide the analyses requested in CQ B10 to explore the potential implications of this assumption.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	See above.
DM = distant metastases; EAG = External Assessment Group; EF = event free; EFS = event-free survival; LRR = locoregional recurrence; TP = transition probability	

Table 1.17: Key issue 16: Relative effectiveness of IO retreatment

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	IO retreatment was allowed in the economic model, while assuming the same relative effectiveness as initial IO treatment. It is uncertain whether this is plausible, or whether the relative effectiveness of IO retreatment would be diminished compared with initial IO treatment. In response to CQ B13, the company acknowledged that "*the model implicitly assumes that the efficacy of IO in these health states (for those patients who are eligible to receive IO) is the same, regardless of whether IO was received in the previous health state*".

Report Section	4.2.6
What alternative approach has the EAG suggested?	Provide the analyses requested in CQ B14 (i.e. assuming that post-recurrence, the relative effectiveness of IO retreatment would be diminished compared with initial IO treatment) to explore the impact of this assumption.
What is the expected effect on the cost effectiveness estimates?	Alternative assumptions can potentially increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	See above.
EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; IO = immuno-oncology	

Table 1.18: Key issue 17: Estimation of the EF utility

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	HRQoL data collected in the AEGEAN trial were analysed using MMRM to estimate the EF health state utility in the economic model. The EAG's concerns relate to 1) the EF utility was informed by the neoadjuvant period of the AEGEAN trial only (i.e. data from the adjuvant period were not used), 2) the EF utility in the company's base-case was higher than the age-adjusted UK general population utility, and 3) missing HRQoL data in the AEGEAN trial.
What alternative approach has the EAG suggested?	As HRQoL data were only gathered during the adjuvant baseline visit and the post-discontinuation follow-up visit, an alternative approach in which the EF utility is based on the AEGEAN trial data is not possible. The EAG capped the EF utility in the EAG base-case to the age-adjusted UK general population norms. In the scenario analysis exploring a lower EF utility, the company could also adjust the other health state utilities relative to the EF utility.
What is the expected effect on the cost effectiveness estimates?	Unclear. The ICER slightly increases (EAG analysis 3). Unclear.
What additional evidence or analyses might help to resolve this key issue?	A scenario analysis using HRQoL data from an alternative perioperative IO treatment in early NSCLC in which also HRQoL data in the adjuvant period was gathered. In the scenario analysis exploring a lower EF utility, the company could also adjust the other health state utilities relative to the EF utility.
EAG = External Assessment Group; EF = event free; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; IO = immune-oncology; MMRM = mixed models for repeated measures; NSCLC = non-small-cell lung cancer; UK = United Kingdom	

Table 1.19: Key issue 18: Proportion of patients receiving IO treatment post-recurrence

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	In the LRR and DM health states, patients were deemed eligible for IO (re)treatment if they received IO treatment in the EF health state and did not progress within 6 months, or did not receive IO in EF, and

Report Section	4.2.9
	had PD-L1 ≤1% (informed by the AEGEAN trial). Of the eligible patients, 70% and 80% of patients were modelled to receive post-recurrence IO for LRR and DM without further progression (DM1), respectively. Based on clinical expert opinion, the EAG questions the appropriateness of using a 6-month progression cut-off to determine eligibility for post-recurrence IO, provided that this is the minimum threshold for funding by NHS England. Clinical experts in the company Advisory Board suggested 6-12 months with a 6 month cut-off being used for the primary analyses. Further, the EAG questions the proportions of eligible patients assumed to receive IO.
What alternative approach has the EAG suggested?	The EAG requested a scenario analysis exploring an alternative cut-off period. The company provided a scenario utilising a 12-month cut-off period, informed by expert opinion. The EAG included this 12-month cut-off period in its EAG analyses. In absence of plausible alternative proportions of eligible patients that receive IO treatment post-recurrence, the EAG also explored a scenario utilising 50% (instead of 70% and 80%) for both LRR and DM post recurrence health states to explore the impact of this input on cost effectiveness results.
What is the expected effect on the cost effectiveness estimates?	Alternative assumptions can potentially increase the ICER. The company's scenario exploring the impact of a 12-month cut-off significantly increased the ICER (for perioperative durvalumab versus neoadjuvant nivolumab + PDC to £23,261).
What additional evidence or analyses might help to resolve this key issue?	The EAG analyses show the relative impact of the company's inputs on cost effectiveness results. Further supportive evidence would help to determine the most accurate inputs for clinical practice in England and Wales.
DM = distant metastases; EAG = External Assessment Group; EF = event free; ICER = incremental cost-effectiveness ratio; IO = immuno-oncology; LRR = locoregional recurrence; NHS = National Health Service; PDC = platinum-doublet chemotherapy; PD-L1 = programmed cell death ligand-1	

Table 1.20: Key issue 19: Advisory Board summary report

Report Section	5.3.1
Description of issue and why the EAG has identified it as important	A summary report was provided for the AEGEAN Health Economic Advisory Board held on 19 January 2024. The company extensively refers to this report/the Advisory Board meeting. The document highlights that the summary report had not been reviewed by the participating clinical advisors. It was also clarified that a full meeting report is yet to be finalised and shared with clinical advisors for review and comment. The EAG has been unable to review the final summary report nor were further materials available (e.g. the meeting presentation slides).
What alternative approach has the EAG suggested?	The EAG wishes to be able to review the finalised report, approved by the participating clinical advisors, as well as other available materials related to the Advisory Board meeting.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses	See above.

Report Section	5.3.1
might help to resolve this key issue?	
EAG = External Assessment Group	

Table 1.21: Key issue 20: Model validation

Report Section	5.3.2
Description of issue and why the EAG has identified it as important	In response to CQ B27, no model comparisons between model outcomes were provided related to: evidence used to develop the economic model, and evidence not used to develop the economic model. To assess the external validity, the EAG would like to see the requested comparisons of model outcomes to external data used, and not used, to develop the economic model.
What alternative approach has the EAG suggested?	In CQ B27, the EAG requested that model outcome validity was assessed through comparisons to: evidence used to develop the economic model, and evidence not used to develop the economic model.
What is the expected effect on the cost effectiveness estimates?	Unclear.
What additional evidence or analyses might help to resolve this key issue?	Provide detailed responses to CQ B27.
CQ = clarification question; EAG = External Assessment Group	

1.6 Summary of the EAG's view

The company's decision problem differed from the NICE Final Scope most significantly in terms of the omission of nCRT as a form of established clinical management (ECM). The EAG considers that nCRT cannot be legitimately excluded until objective evidence that nCRT is less effective than the other included comparators in this population has been provided, and such evidence has not been presented.

The included trial was a high quality double-blind randomised trial where the intervention was identical to that defined in the NICE Final Scope,[1] but the comparator was neoadjuvant placebo given alongside platinum-based chemotherapy with subsequent adjuvant placebo monotherapy. This demonstrated superior EFS, pathological complete response (pCR), and major pathological response (MPR) for the intervention. However, results for DFS were not provided and the non-significant results for OS were not given formal status because of the dictate of the Multiple Testing procedure (MTP). HRQoL [redacted] between intervention and comparator. Part of the reason for these non-significant results, or the inability to present outcome data, is the immaturity of data, related to the current DCO being almost 2 years ago. This leads the EAG to suppose that the company should have waited until the data were more mature before making a submission to NICE. In their current form, the data do not demonstrate efficacy against placebo across all NICE Final Scope[1] outcomes, and it cannot simply be assumed (until the data are presented) that more mature data will show efficacy.

Adverse events (AEs) were described as 'manageable' by the company, but the greater risk of 'deaths possibly related to any study treatment' in perioperative durvalumab compared to perioperative placebo has a relative risk of large magnitude, at 3.47 (95% confidence interval (CI): 0.73, 16.62). The 95% CIs suggest this result may be explained by sampling error, but because of the importance of the adverse

outcome it would probably be prudent to consider the possibility that it represents a real population effect. It should be noted that the AEGEAN statistical analysis plan did not include formal statistical testing for AE results.

The internal validity of these trial results appears to be high, but there are questions about the external validity. For the outcome of EFS, the sub-group analyses suggested there were possible outcome modifiers such as gender and smoking status. Likewise, for the outcome of pCR, the sub-group analyses suggested there were possible outcome modifiers such as for PD-L1 expression, lymph node station, disease stage, smoking status and geographic region. If these characteristics vary between the trial and UK target populations this might prevent the generalisability of findings from trial to UK target population. The company was unable to provide objective data describing the characteristics of the UK target population, relying instead on expert opinion. Hence, it was not possible to exclude differences in potentially effect-modifying characteristics and therefore was not possible to exclude possible threats to external validity.

The trial comparator was not a decision problem comparator, and so the company carried out i) an adjusted matching adjusted indirect comparison (MAIC) (anchored), and ii) an NMA to estimate the effects of the intervention against the decision problem comparators. These ITCs were subject to limitations. Firstly, the only outcome to be used in the MAIC or NMA was EFS, which meant that other outcomes of relevance such as HRQoL, OS or DFS were not considered. One outcome cannot determine the superiority of one treatment over another, given that different outcomes respond differently, and therefore an appraisal of superiority utilising only one outcome is incomplete and invalid. Other limitations were the failure to use one over-riding NMA rather than separate MAICs and an NMA, the lack of consistency testing in the NMA and the failure to use time-dependent HRs. These limitations add some uncertainty to the ITC findings that durvalumab has benefits over the comparators.

The estimated EAG base-case ICERs (probabilistic) versus neoadjuvant nivolumab and PDC, based on the EAG preferred assumptions highlighted in Section 6.1, were £24,177 (cure applied base-case) and £30,694 (no cure applied base-case) per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of 45% and 55% (cure applied base-case), and 35% and 48% (no cure applied base-case) at willingness to pay (WTP) thresholds of £20,000 and £30,000 per QALY gained respectively. The most influential adjustment was applying no cure. The ICER increased most in the scenario analysis with alternative assumptions regarding treatment waning.

There is large remaining uncertainty about the effectiveness and relative effectiveness of perioperative durvalumab as well as IO (re)treatment post-progression, which can be at least partly resolved by the company by conducting further analyses. According to the EAG the current approach (both in the CS and EAG base-case) is suboptimal in terms of model assumptions as well as potential bias due to the state transition approach that both could conceivably change the ICER. Moreover, the current assessment does not provide an appropriate estimation of the comparators listed in the scope. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of perioperative durvalumab compared with all relevant comparators.

Table 1.22: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
CS deterministic base-case (updated following clarification responses)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,897	0.00	0.25
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Fixing error (1-Implementation of AE disutility: remove "/cycles_per_year" from calculation)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,908	0.00	0.25
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Matter of judgement (2-No cure applied)							
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	£2,311	0.06	0.06
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£663	1.06	1.08
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,275	-0.23	0.09
Matter of judgement (3-EF utility capped at age and sex adjusted general population utility)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£20,183	-0.01	0.24
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Matter of judgement (4-Inclusion of wastage costs, i.e. no vial sharing)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,786	0.01	0.25
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Deterministic EAG base-case 1 (Cure applied)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£20,060	0.00	0.24
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Deterministic EAG base-case 2 (No cure applied)							
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£705	1.05	1.06
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,522	-0.24	0.09
Probabilistic EAG base-case 1 (Cure applied)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,177	-0.13	0.13
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Probabilistic EAG base-case 2 (No cure applied)							
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	£12,786	0.03	0.05
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£1,218	0.97	0.99

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£30,694	-0.35	-0.02

AEs = adverse events; CS = company submission; EAG = External Assessment Group; EF = event free; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; PDC = platinum-doublet chemotherapy; WTP = willingness-to-pay

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final Scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the NICE Final Scope	EAG comment
Population	People with untreated resectable NSCLC which has no EGFR or ALK genetic alterations.	Adults with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements.	This submission focuses on the population in line with the anticipated regulatory license and the regulatory trial: *adults with resectable (tumours ≥ 4 cm and/or node-positive) Stage IIA-IIIB [N2] NSCLC and no known EGFR mutations or ALK rearrangements.*	The company's decision problem population is narrower than the NICE scope population, being restricted to those with stage IIA to IIIB cancer. This appears to be due to the anticipated regulatory licence and regulatory trial but means that it will not be possible to extend recommendation of the drug outside this remit.
Intervention	Durvalumab with chemotherapy for neoadjuvant treatment then durvalumab monotherapy for adjuvant treatment.	As per scope.	NA.	None.
Comparator(s)	ECM without durvalumab, which may include: • neoadjuvant nivolumab with chemotherapy • nCRT • platinum-based chemotherapy • active monitoring	ECM without durvalumab, which include: • neoadjuvant nivolumab with chemotherapy • platinum-based chemotherapy • active monitoring Of note, durvalumab is compared with adjuvant platinum-based chemotherapy.	Surgery alone is assumed to represent active monitoring, as such active monitoring is referred to as surgery alone throughout the submission. UK clinical experts, consulted in an Advisory Board, have confirmed that nCRT is not offered to patients with resectable NSCLC in UK clinical practice. nCRT is therefore not	Whilst the EAG accepts that nCRT may not be routinely given in the scope population, this cannot be automatically inferred to mean that nCRT is inferior to perioperative durvalumab in the scope population, and thus eligible for exclusion.

	Final Scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the NICE Final Scope	EAG comment
	• pembrolizumab (subject to NICE appraisal) For people whose tumours express PD-L1 with at least a 50% tumour proportion score • atezolizumab after adjuvant cisplatin-based chemotherapy (subject to NICE appraisal)	Although neoadjuvant chemotherapy is part of the control arm of the regulatory trial AEGEAN, only adjuvant chemotherapy is recommended as a treatment option for some people in UK clinical practice. Clinical experts across the UK were consulted in an Advisory Board confirmed patients are not offered neoadjuvant chemotherapy.	considered a relevant comparator for perioperative durvalumab. Pembrolizumab for adjuvant treatment of resected NSCLC is subject to an ongoing NICE appraisal. Pembrolizumab is therefore not a relevant comparator to durvalumab for this appraisal. Atezolizumab monotherapy is recommended for use within the CDF for adjuvant treatment after complete tumour resection in adult patients with stage IIB or IIIA or N2 only IIIB NSCLC and with PD-L1 expression on ≥50% of TCs and whose disease has not progressed on recently completed adjuvant platinum-based chemotherapy. Atezolizumab is not considered a relevant comparator for adjuvant durvalumab monotherapy because, as per NICE guidelines, new cancer products under appraisal should not include treatments recommended for use in the CDF as comparators. Atezolizumab was also placed at a separate decision point in the Final Scope pathway for ID6234.	The omission of pembrolizumab is because it is still subject to NICE appraisal, which appears reasonable. The company has not included atezolizumab as a comparator for the sub-group expressing PD-L1 with at least a 50% tumour proportion score. This correctly follows NICE methods guidance that states that "*Technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators.*"[2] Surgery alone is taken by the company to represent active monitoring. It is unclear if this implies that surgery alone will always be accompanied by active pre-op and/or post op monitoring, whether surgery itself is deemed a type of active monitoring, or both. In any event, there are more forms of active monitoring

	Final Scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the NICE Final Scope	EAG comment
				than surgery, and these seem to be excluded.
Outcomes	The outcome measures to be considered include: • EFS • DFS • pCR • response rates • OS • adverse effects of treatment • HRQoL	As per scope.	AEGEAN is an ongoing study and per the MTP, DFS and OS will be formally assessed at subsequent interim and final analyses.	None.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into			None.

	Final Scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the NICE Final Scope	EAG comment
	account. The availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	If the evidence allows subgroups will be considered based on: • whether durvalumab is used before and after surgery • PD-L1 tumour proportion score • disease stage	Whilst pre-specified subgroup data from the AEGEAN trial are presented in this submission, including for PD-L1 expression and disease stage (Section B.2.7), the cost effectiveness analysis is based on the full mITT.	In the AEGEAN trial, durvalumab is assessed in the perioperative setting. Participants in the trial were randomised to neoadjuvant durvalumab + PDC followed by adjuvant durvalumab monotherapy versus neoadjuvant placebo + PDC followed by adjuvant placebo. As such, results are presented for the mITT population and not separately for durvalumab used before and after surgery.	None.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			None.

Based on Table 1 and pages 10 to 12 of the CS[3]

ALK = anaplastic lymphoma kinase; CDF = Cancer Drugs Fund; CS = company submission; DFS = disease-free survival; EAG = External Assessment Group; ECM = established clinical management; EGFR = epidermal growth factor receptor; EFS = event-free survival; HRQoL = health-related quality of life; mITT = modified intention-to-treat; MTP = Multiple Testing procedure; N2 = 3-6 cancer cells in nearby nodes; NA = not applicable; NHS = National Health Service; NICE = National Institute of Health and

	Final Scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the NICE Final Scope	EAG comment
Care Excellence; nCRT = neoadjuvant chemoradiotherapy; NSCLC = non-small-cell lung cancer; OS = overall survival; pCR = pathological complete response; PDC = platinum-doublet chemotherapy; PD-L1 – programmed cell death ligand 1; PSS = Personal Social Services; QALY = quality-adjusted life year; TCs = tumour cells; UK = United Kingdom				

2.1 Population

The National Institute for Health and Care Excellence (NICE) Final Scope[1] describes the population as people with untreated resectable non-small-cell lung cancer (NSCLC) which has no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genetic alterations. The company decision problem restricts this population to *" Adults with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements"*. This appears to be due to the anticipated regulatory licence and regulatory trial.

EAG comment: Restriction of the population means that the drug cannot be recommended outside this restriction.

2.2 Intervention

The NICE Final Scope[1] describes the intervention as durvalumab with chemotherapy for neoadjuvant treatment then durvalumab monotherapy for adjuvant treatment. The decision problem is the same.

2.3 Comparators

The NICE Final Scope[1] describes the comparators as established clinical management (ECM) without durvalumab, which may include:

- neoadjuvant nivolumab with chemotherapy
- neoadjuvant chemoradiotherapy (nCRT)
- platinum-based chemotherapy
- active monitoring
- pembrolizumab (subject to NICE appraisal)

The NICE Final Scope[1] adds that for people whose tumours express programmed cell death ligand 1 (PD-L1) with at least a 50% tumour proportion score, the comparator will be atezolizumab after adjuvant cisplatin-based chemotherapy (subject to NICE appraisal). It is unclear if this should be the sole comparator for this sub-group, or additional to those already described.

The company decision problem includes neoadjuvant nivolumab with chemotherapy, platinum-based chemotherapy, and active monitoring. However, it omits nCRT and pembrolizumab, and does not mention atezolizumab after adjuvant cisplatin-based chemotherapy.

EAG comment:

- Surgery alone is taken by the company to represent active monitoring. It is unclear if this implies that surgery alone will always be accompanied by active pre-op and/or post op monitoring, whether surgery itself is deemed a type of active monitoring, or both. In any event, there are more forms of active monitoring than surgery, and these seem to be excluded. The company were asked to clarify[4] what is meant by "*Surgery alone is assumed to represent active monitoring*". The company responded by stating that, "*Surgery alone is deemed to represent a type of active monitoring in resectable patients. It is considered the only relevant representation of active monitoring where no systemic anticancer therapy is given. This approach is consistent with the company submission for TA876.*"[5]
- The External Assessment Group (EAG) require more information on the source of the above statement that surgery alone is the only relevant form of active monitoring for this population.

Without details of the source of information, it is difficult to appraise the validity of the statement. This remains a key issue.

- The omission of pembrolizumab is because it is still subject to NICE appraisal, which appears reasonable.
- The omission of nCRT is made solely because of clinical opinion in the company submission (CS)[3], and further rationale is required. The company were asked to explain the omission, or, if it could not be justified, to include the comparator in all analyses.[4] The company responded by stating that, "*Although neoadjuvant CRT is recommended in NG122 for stage IIIA-N2 patients, this is a small subset of patients equating to roughly 7% of NSCLC patients, which are not typically considered resectable. Duan et al, 2020 demonstrates that the population of patients eligible for neoadjuvant CRT is only about 7% of NSCLC patients and Adizie et al, 2019 reported CRT being administered in only 5% of stage IIIA NSCLC patients in England. Clinicians in attendance at the 2024 UK advisory board unanimously agreed that neoadjuvant CRT is not offered to patients with resectable NSCLC in UK clinical practice. This is further supported by clinical expert opinion gathered for TA876, where neoadjuvant CRT was described as typically being reserved for patients considered to be unresectable. As such, neoadjuvant CRT is not a comparator of interest for this appraisal and is therefore appropriately excluded from comparative clinical and cost-effectiveness analyses*".[5]
- Whilst the EAG accepts that nCRT may not be often given in the scope population, this cannot be automatically inferred to mean that nCRT is inferior to perioperative durvalumab in the scope population, and thus eligible for exclusion. Indeed, infrequent use is also acknowledged in the NICE guideline NG122 and yet it is still recommended to be considered: *"1.7.9 For people with operable stage IIIA–N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider chemoradiotherapy with surgery.* [2019]*"* (p. 20)[6]
- The EAG considers that nCRT cannot be legitimately excluded as a comparator until it can be confirmed that:
    - There is evidence from a direct comparison that nCRT is inferior to perioperative durvalumab in the scope population. Alternatively, if the other comparators are inferior to perioperative durvalumab in the scope population, and nCRT is also inferior or equivalent to the other comparators in the scope population, then nCRT's inferiority to perioperative durvalumab could be indirectly inferred.
    - Previous scientific appraisal of the efficacy of nCRT has not been carried out in the scope population.

If these conditions cannot be shown to apply, then the possibility remains that nCRT may be more effective than perioperative durvalumab, in which case exclusion of nCRT as a comparator might lead to the spurious conclusion that perioperative durvalumab is the most effective treatment available. The company has not provided any evidence that either of these conditions apply. Furthermore, it should be noted that some references were found that suggest that nCRT may actually have some degree of efficacy in the scope population.[7-9] Therefore this remains a key issue.

- The company has not included atezolizumab as a comparator for the sub-group expressing PD-L1 with at least a 50% tumour proportion score. This correctly follows NICE methods guidance that states that "*Technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators.*"[2]
- The trial does not follow the remit of the decision problem, as the trial compares to perioperative placebo (with nCRT). However, an indirect treatment comparison (ITC) is appropriately used to allow comparison of the intervention to some of the decision problem comparators, which is further discussed in Sections 3.3 and 3.4.

2.4 Outcomes

The NICE Final Scope[1] lists the following outcome measures:

- event-free survival (EFS)
- disease-free survival (DFS)
- pathological complete response (pCR)
- response rates
- overall survival (OS)
- adverse effects of treatment
- health-related quality of life (HRQoL)

The decision problem is described as being *per* scope, though it is also implied that DFS and OS will not be formally assessed, per the multiple testing procedure.

EAG comment: DFS and OS are important clinical outcomes, and for a proper assessment these outcomes should be given due prominence. These issues are dealt with further in Sections 3.2.5.2 and 3.2.5.5.

2.5 Other relevant factors

The CS[3] states that, "*Durvalumab is a high-affinity, human, recombinant IgG1κ mAb that selectively binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 receptors. In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity*."

The Food and Drug Administration (FDA) approved durvalumab for patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy on 16 February 2018 [FDA approves durvalumab after chemoradiation for unresectable stage III NSCLC | FDA].

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[3, 10] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[11, 12] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the systematic literature review (SLR) conducted to identify relevant publications reporting the clinical efficacy and safety of perioperative durvalumab and the relevant comparators defined by the NICE Final Scope[1] for the treatment of NSCLC in patients who are candidates for surgical resection.[10] The searches were conducted in July 2022 and updated in October 2023. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-2023/10/27	Original: 27/7/22 Update: 30/10/23
MEDLINE (inc. In Process & ePub ahead of Print and Daily)	Ovid	1946-2023/10/27	Original: 27/7/22 Update: 30/10/23
CENTRAL	Wiley	Up to 2023/10/Issue 10	Original: 27/7/22 Update: 30/10/23
CDSR	Wiley	Up to 2023/10/Issue 10	Original: 27/7/22 Update: 30/10/23
DARE	CRD website	Up to 2015/04/Issue 2	Original: 27/7/22
Conferences			
ASCO	Internet	2021-2023	Original: 27/7/22 Update: 30/10/23
ESMO	Internet	2021-2023	Original: 27/7/22 Update: 30/10/23
ESMO ELCC	Internet	2021-2023	Original: 27/7/22 Update: 30/10/23
ESMO IO Congress	Internet	2020-2022	Original: 27/7/22 Update: 30/10/23
IASLC WCLC	Internet	2021-23	Original: 27/7/22 Update: 30/10/23
IASLC NACLC	Internet	2020-2022	Original: 27/7/22 Update: 30/10/23
AACR	Internet	2021-2023	Original: 27/7/22 Update: 30/10/23

Resource	Host/Source	Date Ranges	Date searched
ESMO Virtual Plenary Sessions	Internet	2020–2023	Original: 27/7/22 Update: 30/10/23
ASCO Virtual Plenary Sessions	Internet	Not reported	Original: 27/7/22 Update: 30/10/23
Trials registries			
www.ClinicalTrials.gov	Internet		Original: 14/10/22 Update: 20/11/23
WHO ICTRP	Internet		Original: 14/10/22 Update: 20/11/23

AACR = American Association for Cancer Research; ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CRD = Centre for Reviews and Dissemination; CS = company submission; DARE = Database of Abstracts of Reviews of Effects; ELCC = European Lung Cancer Congress; ESMO = European Society of Medical Oncology; IASLC = International Association for the Study of Lung Cancer; IO – Immuno-Oncology; NACLC = North America Conference on Lung Cancer; WCLC = World Conference on Lung Cancer; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform

EAG comment:

- Searches were undertaken in July 2022 and updated in October 2023 to identify clinical efficacy and safety of perioperative durvalumab. The CS, Appendix D and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[3, 5, 10]
- A broad range of bibliographic databases, conferences and trials registers were searched. Reference checking was conducted. Searches were well structured, transparent and reproducible.
- The EAG noted that the terms "Stage 1 or Stage I" appeared to be missing from the disease stage facet of the searches. After rerunning a corrected version of the search to confirm that this omission had an affected the recall of results, the EAG asked that the company rerun the searches and screen any records missed by the original strategy. At clarification, the company confirmed that the corrected searches were rerun on 6 March 2024 and that an additional 870 records were screened for relevancy. The company reported that "*no new RCTs or new articles from existing RCTs were identified from these updated searches which would have been considered relevant for the EFS ITC*".[5] Full details of the corrected searches were provided. The company also carried out a comparison of studies included in the CS networks versus Technology Appraisal 876 (TA876) in order to confirm that there were no missing relevant studies.
- The company confirmed and corrected the inclusion of two reporting errors in the Cochrane searches and provided an updated PRISMA flowchart containing the nine hits retrieved by the Cochrane Database of Systematic Reviews (CDSR) not one as previously reported.
- The EAG queried the decision to include a randomised controlled trial (RCT) study design filter in the strategies used to search the Cochrane Central Register of Controlled Trials (CENTRAL) and CDSR resources, which is against current best practice as these are prefiltered resources. The company explained that this was a pragmatic choice, designed to improve the specificity of the searches and one that they did not see having a material impact on the RCTs that were included in the evidence networks for ITCs. Given the breadth of additional searches described the EAG is happy with this explanation.

3.1.2 Inclusion criteria

A SLR conducted on the 27 July 2022 and updated on the 30 October 2023 was performed by the company using RCTs and non-RCTs to identify evidence for the clinical efficacy and safety of perioperative durvalumab for the treatment of resectable NSCLC.

The eligibility criteria used in the search strategy for RCTs is presented in Table 3.2.

Table 3.2: PICO eligibility criteria for the SLR

Category	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years old) with stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC	• Patients without NSCLC • Patients with stage IV NSCLC or metastatic NSCLC • Patients with stage I–III NSCLC who are not candidates for surgical resection of the primary NSCLC (i.e. stage I–III unresectable NSCLC • Children or adolescents (<18 years old)
Intervention	Any or no treatment for stage I–III NSCLC prior to surgical resection of the primary NSCLC	No planned surgical resection of primary NSCLC
Comparators	Any or none[a]	Any or none[a]
Outcomes	Efficacy outcomes, including: • EFS[b] • DFS[b] • OS • MPR • pCR • PFS[b] • RFS[b] • Recurrence rates and recurrence type (including local/regional or distant) Safety outcomes, including: • AEs • Treatment discontinuation or patient withdrawals • Mortality (including perioperative mortality) • Surgical outcomes, including: • Resection rates (including by type of surgical resection) • Complete resection rates/resection margin • Surgical complications • Timing and duration of surgery (including delays to surgery)	• Studies not reporting relevant outcomes • Studies reporting relevant outcomes, but in a mixed population (e.g., patients with stage I–III resectable and unresectable NSCLC) where outcomes are not reported separately for the stage I–III resectable NSCLC population

Category	Inclusion criteria	Exclusion criteria
	HRQoL outcomes, including: • HSUV • HRQoL values	
Study design	RCTs Non-RCTs[c]	Non-interventional studies, including: • Cohort studies • Cross-sectional studies • Case-control studies • Chart reviews • Registries • Case reports/studies Non-primary research publications, including: • Narrative reviews • Editorials • Guidelines • Commentaries • Opinion pieces
	SLR/(N)MAs were considered relevant at the title/abstract review stage and handsearched for relevant primary studies but were excluded during the full-text review stage unless they themselves present original research.	
Other considerations	• Human subjects • Articles with at least the abstract in the English language	• Animal studies • Articles not in the English language

Based on Table 9 of Appendices (Appendix D) of the CS[3]

[a]Studies comparing surgery alone treatment arms (i.e., those without any form of neoadjuvant or adjuvant treatment) were formally included in the initial review but were deprioritised before extraction stage as being of less relevance to the ITC feasibility assessment.

[b]EFS, PFS, DFS and RFS are time-to-event outcomes that may be defined differently and used inter-changeably across studies. EFS and PFS are expected to assess the occurrence of events (e.g. progression, recurrence or death) from randomisation i.e. prior to surgery/from the time of neoadjuvant therapy for study arms that include neoadjuvant therapy. DFS and RFS, on the other hand, are expected to assess the occurrence of events (e.g. recurrence or death) from the time following complete resection in those patients who received surgery. In addition to differences in when outcome measurement begins, there may also be differences in the types of events included (e.g. new primary malignancy in DFS and RFS). The exact definition used in studies was therefore considered as part of the review and was included as part of subsequent extractions. If the definition used in each study was broadly in line with the outcome descriptions provided here, the study was included as part of the review.

[c]Studies with a non-RCT study design were formally included in the initial review but were deprioritised before extraction stage as being of less relevance to the ITC feasibility assessment, given the availability of evidence from RCTs.

AEs = adverse events; CS = company submission; DFS = disease-free survival; EFS = event-free survival; HRQoL = health-related quality of life; HSUV = health state utility values; ITC = indirect treatment comparison; MPR = major pathological response; (N)MA = (network) meta-analysis; NSCLC = non-small-cell lung cancer; OS = overall survival; pCR = pathological complete response; PFS = progression-free survival; PICOS = Population, Intervention, Comparator, Outcomes and Study Design; RCT = randomised controlled trial; RFS = recurrence-free survival; SLR = systematic literature review

EAG comment:

- Regarding the population the SLR protocol is aligned with the decision problem and NICE Final Scope.[1]
- In terms of the comparator, the SLR includes any comparator. This is perhaps broader than the decision problem and NICE Final Scope,[1] and in turn will adequately cover both the decision problem and NICE Final Scope[1] accordingly.
- In terms of the outcomes, the SLR covers all the decision problem and NICE Final Scope[1] outcomes, with the additions of 'surgical outcomes' such as: 'resection rates', 'complete resection rates/resection margin', 'surgical complications', and 'timing and duration of surgery'.
- SLR and (network) meta-analyses ((N)MA) were included during title and abstract screening only, this was to allow for a hand search of the primary studies included. The EAG is satisfied with this approach.
- The SLR only included articles in the English language. Consequently, therefore it is conceivable for the EAG to suggest that potentially meaningful articles could have been missed.

3.1.3 Critique of data extraction

Initially the title and abstracts of studies were screened against the Population, Intervention, Comparators, Outcomes, and Study design (PICOS) eligibility criteria (as outlined in Table 3.2). Screening of all abstracts was performed by two independent reviewers, consensus between both reviewers was undertaken to discuss discrepancies and if necessary, arbitration from a third reviewer if agreement could not be reached. Following title and abstract screening, full-text articles were retrieved and assessed for inclusion by two independent reviewers whilst applying the same PICOS criteria in Table 3.2. Any discrepancies between both independent reviewers were initially discussed and then a final decision was made by a third independent reviewer when required.

Data from included studies were extracted into a pre-specified data extraction grid in Microsoft Excel. Data was initially extracted by a single reviewer, with a second independent reviewer verifying the extracted information and ensuring no relevant information had been missed. Extracted data, included trial/study name, sample, size, study design and interventions (e.g., name, dose and frequency).

EAG comment: The EAG are satisfied that the methodology used in the SLR are adequate.

3.1.4 Quality assessment

A risk of bias analysis was conducted for all 67 (or 68 or 69) included RCTs using the Centre for Reviews and Dissemination (CRD) checklist (Table 3.3).

Table 3.3: Quality assessment results for included RCTs (York CRD checklist)

Study name	Randomisation	Allocation concealment grade	Blinding	Blinding of outcome assessors	Baseline comparability	Follow-up	Selective reporting and other sources of bias	Analysis and statistical methodology
AEGEAN	Y	Y	Y	Y	Y	N	N	N
Albain 2009	Y	Y	NI	NI	PY	Y	Y	N
Altorki 2021	Y	PY	N	N	PY	N	N	Y
Berghmans 2012	Y	Y	NI	NI	Y	N	N	Y
CANOPY-N	Y	Y	N	N	Y	N	N	Y
CheckMate 77T	NI	NI	Y	Y	Y	N	N	Y
CheckMate 816	NI	NI	N	N	PY	N	N	Y
Chen 2013	NI	NI	NI	NI	Y	N	N	N
CHEST	NI	NI	PN	PN	N	NI	PY	Y
De Boer 1999	NI	NI	PN	PN	PY	N	N	PY
Depierre 2002	PY	Y	PN	PN	Y	N	N	PY
Elias 2022	NI	NI	PN	PN	Y	PY	N	PY
EMERGING-CTONG 1103	NI	NI	N	N	PY	N	PN	Y
ESPATUE	NI	NI	NI	NI	PY	N	N	Y
Esteban 2007	NI	NI	NI	NI	PY	Y	N	N
Felip 2000	NI	NI	N	N	Y	N	N	Y
GINEST	NI	NI	NI	NI	PN	N	N	Y
GLCCG01/95	Y	NI	N	N	Y	N	N	Y
Gotti 1994	NI	NI	NI	NI	NI	NI	NI	NI
Hu 2009	NI	NI	PN	PN	NI	NI	NI	PY

Study name	Randomisation	Allocation concealment grade	Blinding	Blinding of outcome assessors	Baseline comparability	Follow-up	Selective reporting and other sources of bias	Analysis and statistical methodology
ID02-327	NI	NI	N	N	NI	Y	N	N
IFCT-0002	Y	Y	N	N	Y	N	PY	Y
IFCT-0101	NI	NI	N	N	Y	N	N	Y
JCOG 0204	Y	NI	N	N	Y	N	N	Y
JCOG 9209	NI	NI	NI	NI	Y	N	N	Y
KEYNOTE-671	Y	NI	NI	PN	Y	Y	N	Y
Kobayashi 2000	NI	NI	NI	NI	Y	NI	NI	N
LCRS	Y	Y	N	Y	Y	N	N	N
Li 2023	NI	NI	N	N	NI	NI	NI	N
Lei, 2020	NI	NI	N	N	NI	NI	N	Y
Li, 2009	NI	NI	NI	NI	Y	N	N	Y
Li, 2012	Y	NI	NI	NI	Y	PN	N	N
Liao, 2003	NI	NI	NI	NI	NI	NI	Y	Y
Lu 2000	NI	NI	NI	NI	NI	NI	N	PY
Masotti 1998	NI	NI	NI	NI	Y	N	N	Y
Matthay 1986	Y	N	PN	PN	Y	PN	PN	PY
Mouritzen 1990	NI	NI	PN	PN	PY	N	N	N
MRC LU22/NVALT 2/EORTC 08012	NI	NI	PN	NI	Y	N	N	Y
NADIM II	NI	NI	NI	Y	NI	NI	PN	Y
NATCH	NI	NI	N	N	Y	N	N	Y
NeoCOAST	NI	NI	N	N	Y	N	N	PY
NeoPredict	NI	NI	N	N	Y	N	N	N

Study name	Randomisation	Allocation concealment grade	Blinding	Blinding of outcome assessors	Baseline comparability	Follow-up	Selective reporting and other sources of bias	Analysis and statistical methodology
NeoSCORE	NI	NI	N	N	Y	N	N	N
NEOSTAR	NI	NI	N	N	Y	Y	N	Y
NEOTORCH	PY	NI	PY	PY	Y	N	N	Y
Pehlivan 2011	PY	NI	NI	NI	NI	N	N	Y
Peng 2004	NI	NI	NI	NI	Y	NI	N	NI
PIT-1	Y	NI	NI	NI	Y	N	N	Y
Pottgen 2007	NI	NI	NI	NI	NI	N	N	Y
RATIONALE-315	NI	NI	NI	Y	Y	N	N	Y
Rosell 1994	PY	NI	N	N	Y	N	N	PY
Roth 1994	Y	NI	N	N	Y	N	N	Y
RTOG 8901	NI	NI	PN	PN	PY	N	N	Y
RTOG-0412	Y	NI	N	N	PY	PY	Y	N
RTOG-0839	NI	NI	N	N	Y	N	N	PN
SAKK 16/00 SWS-SAKK-16/00 EU-20138	Y	Y	N	N	Y	PN	PY	Y
Semik 2004	NI	NI	N	N	Y	N	N	Y
Shepherd 1998	NI	NI	N	N	Y	NI	N	Y
Shukla, 2020	NI	NI	NI	NI	NI	N	N	NA
Sun 2010	Y	NI	NI	NI	Y	N	N	Y
SWOG S9900	Y	NI	N	N	Y	Y	N	Y
TD-FOREKNOW	Y	Y	N	N	Y	N	N	PY
Trakhtenberg 1988	PN	NI	PN	PN	Y	NI	N	N

Study name	Randomisation	Allocation concealment grade	Blinding	Blinding of outcome assessors	Baseline comparability	Follow-up	Selective reporting and other sources of bias	Analysis and statistical methodology
WJTOG9903	NI	NI	PN	PN	Y	PN	N	Y
Yi 2003	NI	NI	PN	PN	PN	NI	NI	PY
Zhao 2016	NI	NI	N	N	Y	N	N	N
Zharkov 1994	NI	NI	NI	NI	NI	NI	PY	NI
Zhou 2001	NI	NI	PN	PN	Y	NI	NI	PY

Based on Table 13 of Appendices (Appendix D) of the CS[10]

Notes:

Randomisation: Was randomisation carried out appropriately?

Allocation concealment grade: Was the concealment of treatment allocation adequate?

Blinding: Were the care providers, participants, and outcome assessors blind to treatment allocation?

Baseline comparability: Were the groups similar at the outset of the study in terms of prognostic factors?

Follow-up: Were there any unexpected imbalances in drop-outs between groups?

Selective reporting and other sources of bias: Is there any evidence to suggest that the authors measured more outcomes than they reported?

Analysis and statistical methodology: Did the analysis include an ITT analysis?

If so, was this appropriate and were appropriate methods used to account for missing data?

CRD = Centre for Reviews and Dissemination; CS = company submission; EORTC = European Organisation for Research and Treatment of Cancer quality of life; ITT = intention-to-treat; N = no; NA = not applicable; NI = no information; PN = partially no; PY = partially yes; RCT: randomised controlled or clinical trial; Y = yes.

EAG comment:

- The company stated in the CS[3] that "*in total across the original SLR and SLR update 132 publications reporting on 67 unique RCTs were prioritised for full data extraction*." Additionally, the company also stated, "*Following the implementation of the evidence prioritisation strategy, which prioritised evidence from RCTs and deprioritised evidence from trials comparing surgery alone treatment arms, 258 (36 update) records were deprioritised, leaving 69 (21 update) articles ultimately undergoing full data extraction*". Whereas, in Table 13 of the Appendices (Appendix D) of the CS[10] 68 RCTs were presented.
- The EAG asked the company to clarify[4] the discrepancy on whether 67, 68 or 69 RCTs were included. The company responded by stating that, "*The statement that "in total across the original SLR and SLR update 132 publications reporting on 67 unique RCTs were prioritised for full data extraction" is correct. This is consistent with the PRISMA in Appendix D.1.2. The inclusion of 68 unique studies in Table 13 of Appendix D is an error. This is due to the incorrect inclusion of the Lei 2020 article (NCT04338620) as a unique study. This article reports from the TD-FOREKNOW study, for which additional publications were identified as part of the updated SLR searches. When including Lei 2020 as a secondary publication for the TD-FOREKNOW study, the number of unique studies is 67. The statement "…leaving 69 (21 update) articles ultimately undergoing full data extraction "refers to the number of articles that were included in the full data extraction during the original SLR searches. This is therefore referring to a different value to the number of unique RCTs identified across both original and updated SLR searches.*"[5] The EAG thanks the company for this clarification, which resolves the confusion.
- The risk of bias analysis was assessed by a single reviewer with conclusions confirmed independently by second reviewer. It was only performed on RCTs, which were given priority over non-RCTs during the data extraction phase.

3.1.5 Evidence synthesis

The database searches returned 5,927 (and 6,576 in the October 2023 update) unique articles from database searches. After removal of duplicated articles between databases (and against the original SLR in the update), 3,653 (589 update) articles were screened at the title and abstract stage, of which 715 (108 updated review) were deemed potentially relevant and screened at the full-text level. Following full-text screening 327 (57 updated review) articles met the inclusion criteria. Evidence was prioritised to include RCTs, leaving "*67 unique RCTs"* which went to full data extraction.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Details of the included trials

Of the 67 RCTs found in the SLR, only one was directly relevant to the decision problem.[13, 14] This RCT is labelled 'AEGEAN' (NCT03800134) and is a double-blind RCT comparing i) neoadjuvant durvalumab with platinum-based chemotherapy, followed by adjuvant durvalumab monotherapy, with ii) neoadjuvant placebo with platinum-based chemotherapy, followed by adjuvant placebo monotherapy. Perioperative durvalumab and perioperative placebo will be the abbreviated terms used to describe the intervention and comparator from now on. The phase 3 trial is ongoing.

The trial comprises 366 patients randomised to perioperative durvalumab, and 374 randomised to perioperative placebo, all of which were in the primary efficacy population (modified intention-to-treat (mITT) cohort) that had no EGFR/ALK gene rearrangements. At the first interim analysis, 156 had completed or discontinued adjuvant durvalumab, and 149 had completed or discontinued adjuvant placebo.

Tables 3.4 and 3.5 below summarise the trial characteristics and the inclusion/exclusion criteria.

Table 3.4: Summary of AEGEAN methodology

Trial number (acronym)	**AEGEAN**
Settings and locations	There were 231 sites in 28 countries across Europe, Asia-Pacific, North America, and South America. There were no UK sites in the trial.
Trial design	AEGEAN is an ongoing[a], phase 3, double-blind, placebo-controlled, randomised, multi-centre, international study.
Eligibility criteria for participants	Eligible patients included adults (≥18 years) with resectable, histologically or cytologically documented, NSCLC (Stage IIA-IIIB (N2); either squamous or non-squamous). Patients must have had no previous treatment for resectable NSCLC. Patients must have a WHO/ECOG PS of 0 or 1 at enrolment, confirmation of tumour PD-L1 status, and be evaluable for EGFR and ALK status.
Sample size	Based on a total of 0.5% alpha allocated to the pCR endpoint, a sample size of approximately 740 eligible patients was planned for the mITT population (randomised 1:1) to provide 55% power to detect a between-arm difference of 12% with a two-sided significance level of 0.008%. Based on a total of 4.5% alpha allocated to the EFS endpoint, for the first interim analysis of EFS and a true overall HR of 0.69, a study with 224 EFS events (per (BICR) in the mITT population (N=740) would provide 50% power to demonstrate an EFS effect with a two-sided significance level of 0.665%. The actual number of randomised patients in the mITT population is 740 with: • n=366 in the perioperative durvalumab arm • n=374 in the perioperative placebo arm
Planned analysis	The mITT population was used for all efficacy and PRO analyses. The type I error was controlled at a 5% 2-sided alpha level using a MTP. This was hierarchical starting with the two primary endpoints of pCR and EFS. The key secondary endpoint of MPR was also planned to be evaluated at the same times as pCR and tested according to an MTP to control the type I error rate. The overall 2-sided 5% type I error was split between pCR (0.5%) and EFS (4.5%) analyses. When statistical significance was demonstrated by pCR and MPR, EFS was tested with an alpha level of 5.0% with alpha recycling. DFS and OS were planned to be evaluated at the same times as EFS and tested according to the MTP. Planned analyses included one interim and one final for pCR, and two interim and one final for EFS:

Trial number (acronym)	AEGEAN
	• the first interim analysis of pCR was planned for when approximately 400 patients in the mITT population had a minimum of 7 months of follow-up (to allow time for surgery and pCR testing by central pathology laboratory). • the first interim analysis of EFS was planned for when approximately 224 EFS events had been reported (approximately 30% maturity in the mITT population)
Trial drugs	Perioperative durvalumab arm (n=366) Durvalumab 1,500 mg IV in combination with platinum-based chemotherapy Q3W for maximum 4 cycles (neoadjuvant period) followed by durvalumab 1,500 mg IV Q4W for maximum 12 cycles (post-surgery period). Perioperative placebo arm (n=374) Placebo IV (saline matching durvalumab volume) in combination with platinum-based chemotherapy Q3W for maximum 4 cycles (neoadjuvant period) followed by placebo IV Q4W for maximum 12 cycles (post-surgery period). The choice of chemotherapy regimen was determined by histology and at the investigator's discretion: • for non-squamous NSCLC: cisplatin + pemetrexed or carboplatin + pemetrexed • for squamous NSCLC: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment)
Permitted and disallowed concomitant medication	Permitted concomitant treatments: • any medication or treatment deemed necessary by the investigators to provide adequate prophylactic or supportive care, excluding disallowed medications • BSC included antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management • PORT was allowed when indicated according to local guidance but PORT could not start until the first post-surgery RECIST 1.1 scan had been completed • disallowed concomitant treatments • any investigational anticancer therapy other than those under investigation in this study • monoclonal antibodies against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study • any concurrent chemotherapy, RT, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study • live attenuated vaccines • immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of

Trial number (acronym)	AEGEAN
	prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers • EGFR TKIs • Herbal anticancer remedies
Method of randomisation and blinding	Patients were randomised 1:1 to the study arms. Prior to randomisation, the investigator recorded the appropriate chemotherapy regimen for the patient in the Interactive Voice/Web Response System. Patients were then centrally randomised and investigator, patients, and study personnel remained blinded to study treatment. Randomisation was stratified by disease stage (stage II versus stage III) and by PD-L1 expression status (TC<1% versus TC≥1%).
Primary outcomes (including scoring methods and timings of assessments)	The AEGEAN study had two primary endpoints: • pCR: defined as the lack of any viable TCs after complete evaluation in the resected lung cancer specimen and all sampled regional lymph nodes and determined according to central pathological review using recommended methods and definitions described by IASLC in 2020 • EFS: defined as the time from randomisation to progression of disease (determined by BICR per RECIST v1.1), death due to any cause, or progression of disease that precludes surgery or discovered while attempting surgery Tumour evaluation was conducted at baseline (prior to randomisation), after completion of neoadjuvant treatment (prior to surgery), post-surgery and prior to the first dose of adjuvant durvalumab/placebo, every 12 weeks for the first year post surgery, and every 24 to 48 weeks thereafter until RECIST 1.1-defined radiological progression of disease, consent withdrawal, or death.
Other outcomes	Secondary • MPR by central laboratory (per IASLC 2020) • DFS using BICR per RECIST 1.1 • OS • pCR, MPR, EFS, DFS, OS in PD-L1 TC ≥1% group • surgical outcomes • HRQoL/PRO (exploratory) • EORTC QLQ-C30, version 3 • EORTC QLQ-LC13 • EQ-5D-5L • safety • AEs, physical examinations, vital signs (including BP, pulse, and ECGs), and laboratory findings (including clinical chemistry, haematology, and urinalysis)
Other outcomes used in the economic model/specified in the scope	The following outcomes are also used in the economic model: • TDT • site of recurrence

Trial number (acronym)	AEGEAN
Pre-planned subgroups	AEGEAN EFS and pCR subgroup analyses included: • age at randomisation (<65 years, ≥65 years) • PD-L1 expression status (<1%, 1-49%, ≥50%) • ECOG PS (0, 1) • race (Asian, non-Asian) • tumour histology (non-squamous, squamous) • smoking status (current, former, never) • disease stage, AJCC 8th Edition (II, III) • chemotherapy at baseline (cisplatin, carboplatin) • lymph node station (N2 single station, N2 multi-station) • geographic region (Asia, Europe, North America, South America)
Based on Table 5, CS[3] aAEGEAN is an ongoing study and per the MTP, DFS and OS will be formally assessed at subsequent interim and final analyses. EFS efficacy data continues to be collected, AstraZeneca remains blinded to DFS, and the study continues in a blinded manner with patients and investigators blinded to treatment assignment AEs = adverse events; AJCC = American Joint Committee on Cancer; ALK = anaplastic lymphoma kinase; BICR = Blinded Independent Central Review; BP = blood pressure; BSC = best supportive care; CS = company submission; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; DFS = disease-free survival; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer 13-item Lung Cancer Quality of Life Questionnaire; EQ-5D-5L = EuroQol 5-Dimension, 5-Level health state utility index; HR = hazard ratio; HRQoL = health-related quality of life; IASLC = International Association for the Study of Lung Cancer; IV = intravenous; mITT = modified intention-to-treat; MPR = major pathological response; MTP = Multiple Testing procedure; N2 = 3-6 cancer cells in nearby nodes; NSCLC = non-small-cell lung cancer; OS = overall survival; pCR = pathological complete response; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand-1; PORT = post-operative radiation therapy; PRO = patient-reported outcome; PS = Performance Status; Q3W = every 3 weeks; Q4W = every 4 weeks; RECIST = Response Evaluation Criteria in Solid Tumours; RT = radiotherapy; TC = tumour cells; TDT = time to discontinuation of treatment; TKI = tyrosine kinase inhibitor; UK = United Kingdom; WHO = World Health Organization	

Table 3.5: Key eligibility criteria for AEGEAN

Eligibility Criteria
Inclusion criteria
• Male or female, age ≥18 years. • Newly diagnosed and previously untreated patients with histologically or cytologically documented NSCLC with resectable (stage IIA to select (i.e., N2) stage IIIB) disease. • A WHO/ECOG PS of 0 or 1 at enrolment. • At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 Target Lesion at baseline. • No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.

Eligibility Criteria
• Adequate organ and marrow function. • Confirmation of a patient's tumour PD-L1 status. • Provision of sufficient tumour biopsy sample for evaluation and confirmation of EGFR and ALK status. • Planned surgery must comprise lobectomy, sleeve resection, or bilobectomy as determined by the attending surgeon. • Adequate cardiac and lung function. • Life expectancy of at least 12 weeks.
Exclusion criteria
• History of allogeneic organ transplantation. • Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome). • History of another primary malignancy. • History of active primary immunodeficiency. • Uncontrolled intercurrent illness. • Active infection including tuberculosis hepatitis B and C, or human immunodeficiency virus. • Deemed unresectable NSCLC by multidisciplinary evaluation. • Patients who have pre-operative RT treatment as part of their care plan. • Patients who have brain metastases or spinal cord compression. • Stage IIIB N3 and Stages IIIC, IVA, and IVB NSCLC. • Mean QTcF ≥470 ms calculated from up to three ECGs (within 30 minutes). • Known allergy or hypersensitivity to any of the study drugs or excipients. • Existence of more than one primary tumour such as mixed small cell and NSCLC histology. • Patients whose planned surgery at enrolment includes any of the following procedures: pneumonectomy, segmentectomies, or wedge resections. • Any medical contraindication to treatment with platinum-based doublet chemotherapy as listed in the local labelling. • Patients with a documented test result confirming the presence of EGFR mutation or ALK translocation.
Based on Table 6, CS[3] ALK = anaplastic lymphoma kinase; CS = company submission; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; N2 = 3-6 nearby nodes in nearby nodes; N3 = >7 cancer cells in nearby nodes; NSCLC = non-small-cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand-1; PD-L2 = programmed cell death ligand-2; PS = Performance Status; QTcF = QT interval (time from start of Q wave to end of the T wave) corrected for heart rate by Fridericia's cube root formula; RECIST = Response Evaluation in Solid Tumours; RET = radiotherapy; WHO = World Health Organization

3.2.2 Statistical analysis of the included trials

Table 3.6 summarises the study group definitions.

Table 3.6: Study group definitions in AEGEAN

Population	Definition
ITT	All randomised patients
mITT[a]	ITT excluding patients with documented EGFR/ALK aberrations
pCR IA cohort	First ~400 patients in the mITT
Safety analysis set	ITT patients who received ≥1 dose of study treatment

[a]Patients with EGFR/ALK gene arrangements were analysed in a separate study
ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; IA = interim analysis; ITT = intention to treat; mITT = modified intention to treat; pCR = pathological complete response

This was a superiority trial, restricted to the mITT population. Type I error rate was controlled by a hierarchical Multiple Testing procedure (MTP), where an overall 2-sided 5% error rate is split between the two primary end-points. The CS[3] describes the general statistical methods as follows: "*For pathological endpoints, response rates were compared between treatment arms using a stratified Cochran-Mantel-Haenszel test. The treatment effect was estimated by the differences in response rates, with their corresponding 95% confidence intervals (CIs) calculated by the stratified Miettinen and Nurminen method.20 Event-free survival was compared between the treatment arms using a stratified log-rank test, with the treatment effect estimated by HRs and 95% CIs calculated with stratified Cox-proportional-hazards models. Medians and landmark rates for EFS were estimated using the Kaplan-Meier (KM) method*."

EAG comment: Statistical approaches are appropriate.

3.2.3 Baseline characteristics of the included trials

Table 3.7 summarises key patient demographics and baseline characteristics, and Table 3.8 summarises the disease characteristics in each arm. The CS[3] stated that arms were well-balanced, the exception being a small imbalance for sex.

Table 3.7: Key patient demographics and baseline characteristics in AEGEAN

Characteristic	Perioperative durvalumab n=366	Perioperative placebo n=374
Median age, years (range)	65 (30–88)	65 (39–85)
≥75 years, n (%)	44 (12.0)	36 (9.6)
Male gender, n (%)	252 (68.9)	278 (74.3)
Race, n (%)		
Asian	143 (39.1)	164 (43.9)
White	206 (56.3)	191 (51.1)
Other	17 (4.6)	19 (5.1)
Region, n (%)		
Asia	142 (38.8)	163 (43.6)
Europe	141 (38.5)	140 (37.4)
North America	43 (11.7)	43 (11.5)
South America	40 (10.9)	28 (7.5)

Characteristic	Perioperative durvalumab n=366	Perioperative placebo n=374
Smoking status, n (%)		
Never	51 (13.9)	56 (15.0)
Former	220 (60.1)	223 (59.6)
Current	95 (26.0)	95 (25.4)

Based on Table 11, CS[3]
CS = company submission; n = number in sample

Table 3.8: Key disease characteristics in AEGEAN

Characteristic	Perioperative durvalumab n=366	Perioperative placebo n=374
ECOG PS, n (%)		
0	251 (68.6)	255 (68.2)
1	115 (31.4)	119 (31.8)
AJCC stage[a] at diagnosis, n (%)		
II	104 (28.4)	110 (29.4)
IIIA	173 (47.3)	165 (44.1)
IIIB	88 (24.0)	98 (26.2)
Histology type, n (%)		
Squamous	169 (46.2)	191 (51.1)
Non-squamous	196 (53.6)	179 (47.9)
TNM classification		
Primary tumour, n (%)		
T1	44 (12.0)	43 (11.5)
T2	97 (26.5)	108 (28.9)
T3	128 (35.0)	129 (34.5)
T4	97 (26.5)	94 (25.1)
Regional lymph nodes, n (%)	[redacted]110 (30.1)	[redacted]102 (27.3)
N0	75 (20.5)	87 (23.3)
N1	181 (49.5)	185 (49.5)
N2		
PD-L1 expression, n (%)		
TC <1%	122 (33.3)	125 (33.4)
TC 1-49%	135 (36.9)	142 (38.0)
TC ≥50%	109 (29.8)	107 (28.6)
Planned neoadjuvant platinum agent, n (%)		
Cisplatin	100 (27.3)	96 (25.7)
Carboplatin	266 (72.7)	278 (74.3)

Based on Table 12, CS.[3]
[a]AJCC 8th Edition
AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; N0 = no cancer cells in nearby nodes; N1 = 1-2 cancer cells in nearby nodes; N2 = 3-6 cancer cells in nearby nodes; PD-L1 = programmed cell death ligand-1; PS = Performance Status; T1 = cancer contained within the lung; T2 = cancer

Characteristic	Perioperative durvalumab n=366	Perioperative placebo n=374
between 3 cm and 5 cm across or with specific features; T3 = cancer between 5 cm and 7 cm or involving specific structures; T4 = cancer bigger than 7 cm or spread into other structures; TC = tumour cells; TNM = tumour-node-metastasis		

EAG comment:

- The arms appeared to be well balanced, with no systematic favouring of one arm over the other.
- The baseline characteristics are of the whole randomised cohort, but because only a proportion of patients had completed adjuvant treatment, this does not necessarily represent the patients for whom outcome data are reported. The company were asked[4] to provide the baseline characteristics for the patients participating in the specific data cut-off (DCO) points relating to the reported outcome data.
- The company responded by stating that, "*Baseline characteristics for the modified intent-to-treat (mITT) are presented in the CS. The mITT population included all randomised patients, excluding those whose tumours have known epidermal growth factor receptor mutations (EGFRm) or anaplastic lymphoma kinase (ALK) gene rearrangements. Unless otherwise specified, the mITT population or subsets of the mITT population were used for all efficacy analyses, including patient-reported outcomes (PROs). Treatment arms were compared on the basis of randomised study treatment, regardless of the treatment actually received. Patients who were randomised but did not subsequently go on to receive study treatment were included in the analysis in the treatment arm to which they were randomised. The baseline characteristics presented for outcomes at the first interim analysis (IA1) of EFS, therefore, are the same as those for whom outcome data are reported at the D120SU. The only discrepancy in baseline characteristics for presented outcomes is for the 14 January 2022 DCO, where pathological complete response (pCR) was analysed, as not all patients had been randomised at this point in time. This analysis was planned to be conducted after approximately 400 patients in the mITT population had a minimum opportunity for follow-up of approximately 7 months prior to DCO in order to allow time for surgery and pCR assessment by a central pathology laboratory to occur (interim ITT cohort). The baseline patient and disease characteristics for the mITT population at EFS IA1, the D120SU, and pCR IA1 are presented in Table 3.9 and Tables 3.10.*"[5]
- The EAG thanks the company for the clarification above and acknowledges that the baseline comparability at pCR interim analysis 1 (IA1) is generally similar to comparability at the other two time-points.

Table 3.9: Baseline patient characteristics in AEGEAN, mITT population at EFS IA1, D120SU, and pCR IA1

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	**Perioperative placebo n=374**	**Perioperative durvalumab n=366**	**Perioperative placebo n=374**	**Perioperative durvalumab n=196**	**Perioperative placebo n=206**
Median age, years (range) ≥75 years, n (%)	65 (30–88) 44 (12.0)	65 (39–85) 36 (9.6)	65 (30–88) 44 (12.0)	65 (39–85) 36 (9.6)	[redacted]	[redacted]
Characteristic	252 (68.9)	278 (74.3)	252 (68.9)	278 (74.3)	[redacted]	[redacted]
Race, n (%) Asian White Other	143 (39.1) 206 (56.3) 17 (4.6)	164 (43.9) 191 (51.1) 19 (5.1)	143 (39.1) 206 (56.3) 17 (4.6)	164 (43.9) 191 (51.1) 19 (5.1)	[redacted]	[redacted]
Region, n (%) Asia Europe North America South America	142 (38.8) 141 (38.5) 43 (11.7) 40 (10.9)	163 (43.6) 140 (37.4) 43 (11.5) 28 (7.5)	142 (38.8) 141 (38.5) 43 (11.7) 40 (10.9)	163 (43.6) 140 (37.4) 43 (11.5) 28 (7.5)	[redacted]	[redacted]

Smoking status, n (%) Never Former Current	51 (13.9) 220 (60.1) 95 (26.0)	56 (15.0) 223 (59.6) 95 (25.4)	51 (13.9) 220 (60.1) 95 (26.0)	56 (15.0) 223 (59.6) 95 (25.4)	[redacted]	[redacted]
Based on Table 8, Company response to clarification[5] D120SU = day 120 safety update; EFS = event-free survival; IA1 = interim analysis 1; mITT = modified intention-to-treat; pCR = pathological complete response						

Table 3.10: Baseline disease characteristics in AEGEAN, mITT population at EFS IA1, D120SU, and pCR IA1

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	**Perioperative placebo n=374**	**Perioperative durvalumab n=366**	**Perioperative placebo n=374**	**Perioperative durvalumab n=196**	**Perioperative placebo n=206**
ECOG PS, n (%) 0 1	251 (68.6) 115 (31.4)	255 (68.2) 119 (31.8)	251 (68.6) 115 (31.4)	255 (68.2) 119 (31.8)	[redacted]	[redacted]
AJCC stage[a] at diagnosis, n (%) II IIIA IIIB	104 (28.4) 173 (47.3) 88 (24.0)	110 (29.4) 165 (44.1) 98 (26.2)	104 (28.4) 173 (47.3) 88 (24.0)	110 (29.4) 165 (44.1) 98 (26.2)	[redacted]	[redacted]
Histology type, n (%) Squamous Non-squamous	169 (46.2) 196 (53.6)	191 (51.1) 179 (47.9)	169 (46.2) 196 (53.6)	191 (51.1) 179 (47.9)	[redacted]	[redacted]

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	**Perioperative placebo n=374**	**Perioperative durvalumab n=366**	**Perioperative placebo n=374**	**Perioperative durvalumab n=196**	**Perioperative placebo n=206**
TNM classification					[redacted]	[redacted]
Primary tumour, n (%)	44 (12.0)	43 (11.5)	44 (12.0)	43 (11.5)		
T1	97 (26.5)	108 (28.9)	97 (26.5)	108 (28.9)		
T2	128 (35.0)	129 (34.5)	128 (35.0)	129 (34.5)		
T3	97 (26.5)	94 (25.1)	97 (26.5)	94 (25.1)		
T4	[redacted]110 (30.1)	[redacted]102 (27.3)	[redacted]110 (30.1)	[redacted]102 (27.3)		
Regional lymph nodes, n (%)	75 (20.5)	87 (23.3)	75 (20.5)	87 (23.3)		
N0	181 (49.5)	185 (49.5)	181 (49.5)	185 (49.5)		
N1						
N2						

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	**Perioperative placebo n=374**	**Perioperative durvalumab n=366**	**Perioperative placebo n=374**	**Perioperative durvalumab n=196**	**Perioperative placebo n=206**
PD-L1 expression, n (%) TC <1% TC 1-49% TC ≥50%	122 (33.3) 135 (36.9) 109 (29.8)	125 (33.4) 142 (38.0) 107 (28.6)	122 (33.3) 135 (36.9) 109 (29.8)	125 (33.4) 142 (38.0) 107 (28.6)	[redacted]	[redacted]
Planned neoadjuvant platinum agent, n (%) Cisplatin Carboplatin	100 (27.3) 266 (72.7)	96 (25.7) 278 (74.3)	100 (27.3) 266 (72.7)	96 (25.7) 278 (74.3)	[redacted]	[redacted]

	EFS IA1		D120SU		pCR IA1	
	Perioperative durvalumab n=366	**Perioperative placebo n=374**	**Perioperative durvalumab n=366**	**Perioperative placebo n=374**	**Perioperative durvalumab n=196**	**Perioperative placebo n=206**

Based on Table 9, Company response to clarification[5]

[a]AJCC 8th Edition

AJCC = American Joint Committee on Cancer; D120SU = day 120 safety update; EFS = event-free survival; ECOG = Eastern Cooperative Oncology Group; IA1 = interim analysis 1; PD-L1 = programmed cell death ligand-1; TNM = tumour-node-metastasis; mITT = modified intent-to-treat; N0 = no cancer cells in nearby nodes; N1 = 1-2 cancer cells in nearby nodes; N2 = 3-6 cancer cells in nearby nodes; pCR = pathological complete response; PS = Performance Status; TC = tumour cells; T1 = cancer contained within the lung; T2 = cancer between 3 cm and 5 cm across or with specific features; T3 = cancer between 5 cm and 7 cm or involving specific structures; T4 = cancer bigger than 7 cm or spread into other structures

3.2.4 Risk of bias in the included trials

Table 3.11 summarises the quality assessment results for the AEGEAN trial.

Table 3.11: Quality assessment results for AEGEAN

Domain	Grade (yes/no/unclear)	Details
Was the randomisation method adequate?	Yes	Block randomisation stratified by disease stage (stage II versus III) and PD-L1 expression (<1% versus >=1%).
Was the concealment of treatment allocation adequate?	Yes	Assigned via interactive voice/web recognition system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics were similar between both treatment arms, but no formal analysis was reported.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	AEGEAN is a double-blind trial; the primary endpoint of EFS was assessed in a blinded fashion by independent central review.
Were there any unexpected imbalances in drop-outs between groups?	No	There were no imbalances or unexpected drop outs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were reported for data which were available.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	AEGEAN included an ITT analysis; however, the mITT population was used for the primary efficacy analysis. Patients were removed as they were not eligible according to a protocol amendment.
Based on Table 14, CS[3] CS = company submission; EFS = event-free survival; ITT = intention-to-treat; mITT = modified intention-to-treat; PD-L1 = programmed cell death ligand-1		

EAG comment:

- After reading the published trial report[14] and published trial protocol,[15] levels of selection bias were unclear. Firstly, the precise method of randomisation was unclear; stating that groups were 'randomised' does not tell the reader that the methods used were valid. Secondly, there was no mention of any method of allocation concealment: certainly, an interactive voice/web recognition system did not appear to be mentioned. The company were asked[4] to provide the documentation that confirms the use of allocation concealment.
- The company responded by stating that, "*The use of an interactive voice/web recognition system (IXRS) is described in the published protocol and its use for the randomisation and allocation concealment is described in more detail in the AEGEAN Clinical Study Report (CSR). A unique randomization number was then obtained via the IXRS and patients were centrally assigned to one of the 2 treatment arms in a 1:1 ratio. Assignment to durvalumab versus placebo was determined by the randomisation scheme in the IXRS. A blocked*

randomisation was generated, and all centres used the same list in order to minimise any imbalance in the number of patients assigned to each treatment arm."[5]

- In relation to the company response, the EAG thanks the company for the new references that confirm the use of the IXRS and the method of randomisation in the trial.

3.2.5 Efficacy results in the included trials

All outcomes in the NICE Final Scope[1] and decision problem were included in the trial (although DFS was not reported). Additionally, 'surgical outcome' was reported in the trial; this has not been included in the EAG report because it is not listed in the decision problem.

EAG comment:

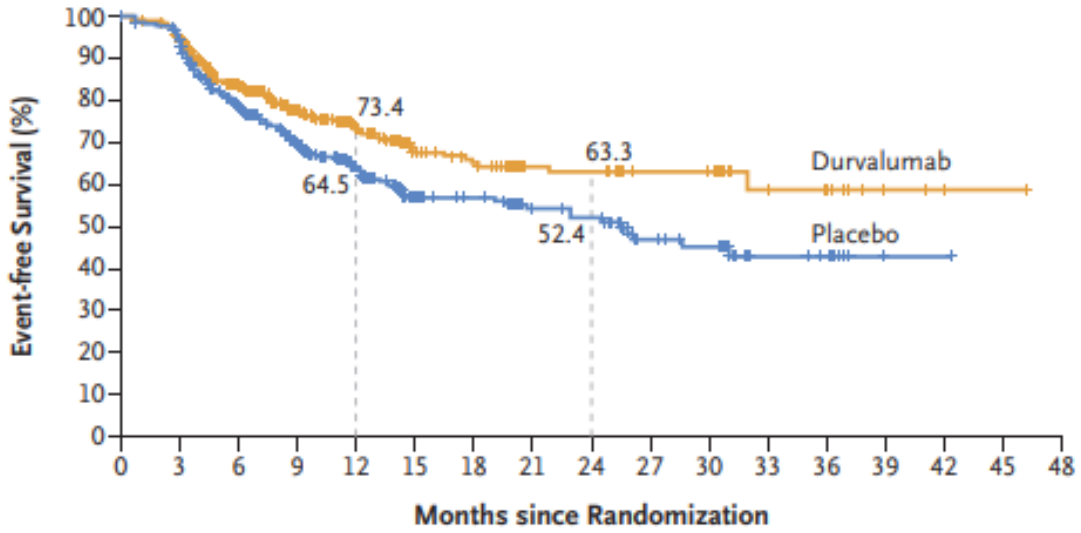
- The most recent DCO for clinical efficacy outcomes was November 2022, despite this being over 16 months ago. The company were asked[4] to explain why a more recent DCO was not used, to provide data for a more recent DCO if possible and to redo all analyses if needed.
- The company responded by stating that, "*The 10 November 2022 DCO is the most recent planned analysis for the AEGEAN trial following multiple testing procedure (MTP). As stated in the CS, a safety update was provided to the US Food and Drug Administration (FDA) review as part of regulatory procedures (DCO [redacted]). It was agreed with the FDA that overall survival (OS) would be unblinded and provided at the time of the safety update to support benefit-risk assessment. The day 120 safety update (D120SU), therefore, is limited to safety outcomes and overall survival. A second planned interim analysis containing a more extensive set of outcomes is expected to become available later in 2024, when EFS data is at approximately 40% maturity.*"[5]
- The EAG thanks the company for this clarification. However, the EAG wonders why the submission was not delayed until later in 2024, when EFS data is at approximately 40% maturity.

3.2.5.1 EFS

The CS[3] defines EFS as "*the time from randomisation to an event of disease progression that precludes surgery, local or distant recurrence, or death due to any cause*".

For the primary analysis DCO on 10 November 2022 (N=740), treatment with perioperative durvalumab resulted in a statistically significant improvement in EFS compared with perioperative placebo, with a 32% reduction in the risk of an EFS event for the perioperative durvalumab arm compared to the perioperative placebo arm. A hazard ratio (HR) of 0.68 (95% confidence interval (CI) 0.53 to 0.88; p=0.004) was calculated. Figure 3.1 shows the Kaplan-Meier (KM) plot.

Figure 3.1: KM plot of EFS, mITT population



	No. of Events/ No. of Patients	Median Event-free Survival (95%CI)
		mo
Durvalumab	98/366 (26.8)	NR (31.9–NR)
Placebo	138/374 (36.9)	25.9 (18.9–NR)

Stratified hazard ratio for disease progression, recurrence, or death, 0.68 (95% CI, 0.53–0.88)
P=0.004 by stratified log-rank test

No. at Risk

Durvalumab	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
Placebo	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

Based on Figure 5, CS[3]

Note: durvalumab and placebo refers to the perioperative durvalumab and the perioperative placebo arms in AEGEAN.

CI = confidence interval; CS = company submission; DCO = data cut-off; EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat; NR = not reached

3.2.5.2 DFS

Disease-free survival is defined as "the time from resection until local or distant disease recurrence in the subpopulation of patients who were disease-free following resection, or death due to any cause, whichever occurs first". No results are provided for this outcome, despite being reported by the CS[3] to have been "formally tested at the primary analysis of EFS (DCO 10 November 2022)". The rationale provided in the CS[3] was that it "did not meet the prespecified boundary to declare statistically significance".

EAG comment:

- There is insufficient rationale in the CS[3] for the failure to present an outcome that was prescribed by the NICE Final Scope[1] and agreed to in the decision problem. The company were asked[4] to give a rationale for why the analysis was not reported, and to present the findings for this outcome.
- The company responded by stating that, "*Disease-free survival (DFS) was tested by the independent data monitoring committee at the primary analysis of EFS (EFS IA1, DCO 10 November 2022) and did not meet the prespecified boundary to declare statistically significant. Therefore, as per the MTP, which consists of a hierarchical gatekeeping strategy, DFS was not reported at EFS IA1 and the study team remain blinded to DFS to preserve the integrity of the outcome. Disease-free survival will be tested when EFS data is at approximately 40% maturity (second interim analysis), in line with the MTP*."[5]
- In relation to the response above, the EAG understands that, per the rigorous MTP, the first interim analysis with a statistical analysis for DFS would only occur when there were 400 patients with a minimum of 7 months follow-up. However, the EAG does not understand why the raw DFS data could not have been reported without statistical analysis by an independent unblinded team distinct from the blinded study team, given that DFS is an outcome decreed by NICE and therefore of relevance for the committee. This remains a key issue.

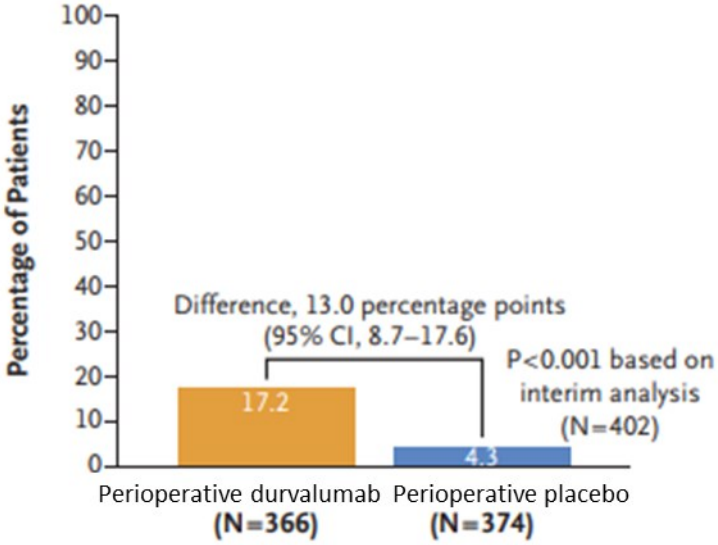
3.2.5.3 pCR

The CS[3] defines pCR as, "*the proportion of patients who have a lack of any viable tumour cells after complete evaluation in the resected lung cancer specimen and all sampled regional lymph nodes*".

For the primary analysis of pCR at DCO on 14 January 2022 (N=402), treatment with perioperative durvalumab resulted in a significant improvement in pCR compared with perioperative placebo. A higher pCR rate of 17.9% was observed for patients in the perioperative durvalumab arm versus 4.9% in the perioperative placebo arm. This resulted in a treatment difference in proportions of 13.0% (95% CI 7.1 to 19.5; $p<0.001$)

For the final analysis DCO on 10 November 2022 (N=740), treatment with perioperative durvalumab resulted in a significant improvement in pCR compared with perioperative placebo with a difference in proportions of 13.0% (95% CI 8.7 to 17.6). Figure 3.2 summarises the final analysis results.

Figure 3.2: pCR at final analysis, mITT population



Based on Figure 6, CS[3]
CI = confidence interval; CS = company submission; DCO = data cut-off; mITT = modified intention-to-treat; pCR = pathological complete response

EAG comment:

- Results are given at both the primary data analysis point and the final analysis point for this pCR outcome, whereas they are only given for the primary analysis point for EFS. The company were asked[4] to clarify the reasons for this.
- The company responded by stating that, "*As specified in the trial protocol, one interim analysis was planned for pCR, when all patients in the ITT population had the opportunity to undergo surgery (i.e., ~7 months follow-up) and complete central pathology assessment (DCO 14 January 2022). A first interim analysis of EFS was planned to occur when approximately 224 EFS events have occurred (approximately 30% maturity in the mITT). The first interim analysis of EFS coincided with the final analysis of pCR (DCO 10 November 2022). Thus, there was no analysis of EFS at the time of the interim pCR analysis (DCO 14 January 2022).*"[5]
- The EAG thanks the company for the above clarification.

3.2.5.4 Response Rates

Three 'response rate' outcomes were covered in the CS[3]: MPR, pathological regression and objective response rate (ORR). These are reported below.

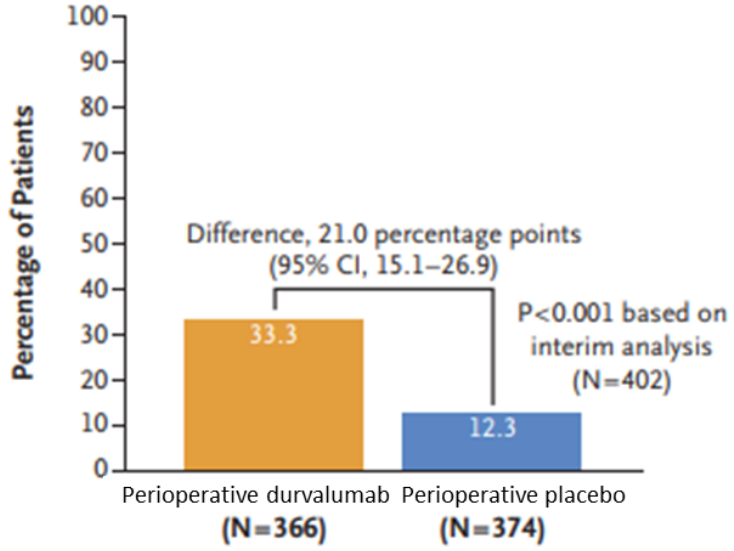
3.2.5.4.1 MPR

MPR was defined by the CS[3] as *"≤10% viable tumour cells in lung primary tumour after complete evaluation in the resected lung cancer specimen"*.

At the primary 14 January 2022 cut-off, there was a statistically significant improvement in MPR for the perioperative durvalumab arm compared with the perioperative placebo arm (34.2% versus 14.1%, respectively) resulting in a significant difference in proportions of 20.1% (95% CI 11.8 to 28.3; p<0.001).

At the final analysis on 10 November 2022, the treatment difference in proportions for the perioperative durvalumab arm versus the perioperative placebo arm was 21.0% (33.3% versus 12.3%, respectively; 95% CI 15.1 to 26.9). Figure 3.3 summarises the 10 November 2022 analysis results.

Figure 3.3: MPR at final analysis, mITT population on 10 November 2022



Based on Figure 9, CS.[3]
CI = confidence interval; CS = company submission; DCO - data cut-off; mITT = modified intention-to-treat; MPR = major pathological response

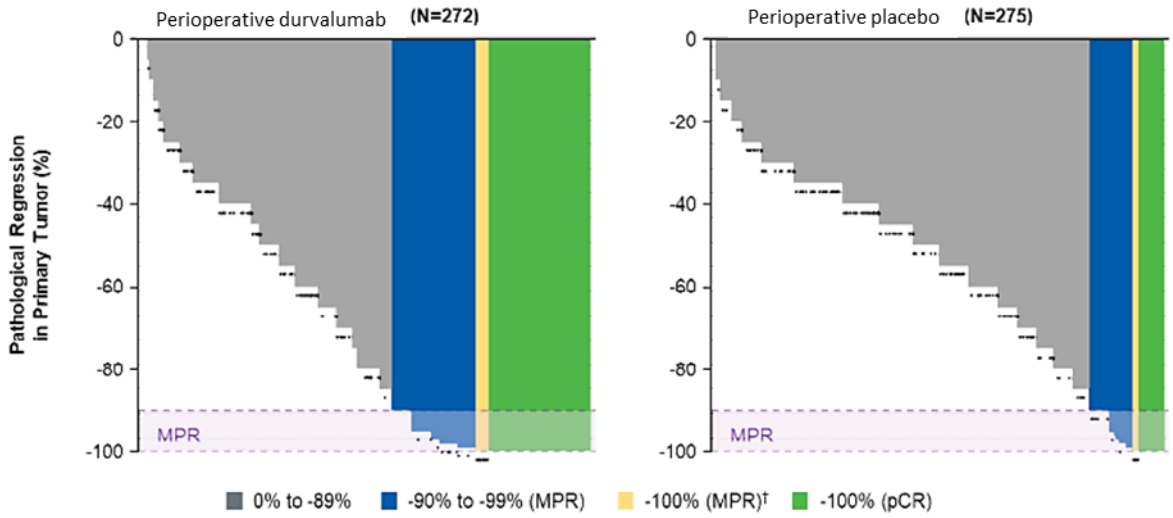
EAG comment:

- Results are given at both the primary data analysis point and the final analysis point for this MPR outcome, whereas they are only given for the primary analysis point for EFS. The company were asked[4] to clarify the reasons for this.
- The company responded by stating that, "*As specified in the trial protocol, one interim analysis was planned for pCR, when all patients in the ITT population had the opportunity to undergo surgery (i.e., ~7 months follow-up) and complete central pathology assessment (DCO 14 January 2022). A first interim analysis of EFS was planned to occur when approximately 224 EFS events have occurred (approximately 30% maturity in the mITT). The first interim analysis of EFS coincided with the final analysis of pCR (DCO 10 November 2022). Thus, there was no analysis of EFS at the time of the interim pCR analysis (DCO 14 January 2022).*"[5]
- The EAG thanks the company for the above clarification.

3.2.5.4.2 Pathological regression

Pathological regression was defined by the CS[3] as, *"% viable tumour cells minus 100%."* At the 10 November 2022 DCO, the perioperative durvalumab arm showed greater pathological regression of the primary tumour than the perioperative placebo arm, with wider proportions of patients achieving MPR and pCR in the waterfall plot in Figure 3.4.

Figure 3.4: Pathological regression, mITT population



Based on Figure 10, CS[3]

*Indicates patients with evidence of carcinoma present in any examined lymph nodes or whose lymph nodes are not evaluable.

†Patients with no viable tumour cells in the primary tumour, but with evidence of carcinoma present in examined lymph nodes, or whose lymph nodes are not evaluable, are classified as responders for MPR and non-responders for pCR, in accordance with the definitions of these endpoints.

CS = company submission; DCO = data cut-off; mITT = modified intention-to-treat; MPR = major pathological response; pCR = pathological complete response

EAG comment: No statistical analysis was performed for this outcome.

3.2.5.4.3 Objective response rate (ORR)

The CS[3] defined ORR as "*the percentage of patients with a complete response or partial response at their latest assessment prior to surgery*". This was evaluated prior to surgery on 10 November 2022, without a pre-defined study endpoint. More patients in the perioperative durvalumab arm achieved a complete or partial response than the perioperative placebo arm (56.3% and 38.0% respectively). Table 3.12 summarises the results.

Table 3.12: ORR prior to surgery (BICR RECIST v1.1), mITT population

Response	Perioperative durvalumab n=366	Perioperative placebo n=374
ORR, n (%)	206 (56.3)	142 (38.0)
95% CI	51.0-61.4	33.0-43.1
Patients with a response, n (%)		
Complete	4 (1.1)	1 (0.3)
Partial	202 (55.2)	141 (37.7)
No response, n (%)		
Stable disease	124 (33.9)	189 (50.5)
Progression	11 (3.0)	15 (4.0)
Not evaluable[a]	25 (6.8)	28 (7.5)

Based on Table 16, CS[3]

[a] Includes patients with missing baseline scans or missing pre-surgery scans

Response	Perioperative durvalumab n=366	Perioperative placebo n=374

BICR = Blinded Independent Central Review; CI = confidence interval; CS = company submission; mITT = modified intention-to-treat; ORR = objective response rate; RECIST = Response Evaluation in Solid Tumours

EAG comment:

- No statistical analysis was performed for the ORR outcome. The company were asked[4] to provide one.
- The company responded by stating that, "*The objective response rate (ORR) is reported in section B.2.6.3.4 of the CS. As stated in the CS, this outcome was evaluated in the mITT population prior to surgery using blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and was not a pre-defined study endpoint. The analysis of ORR was performed on the mITT population using a Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors from IXRS, disease stage (Stage II vs Stage III) and programmed cell death ligand-1 (PD-L1) expression status (tumour cells [TC] < 1% vs TC ≥ 1%). The effect of treatment was estimated by the difference in proportions between treatment arms, together with their corresponding confidence interval (CI) and p-value from the CMH test. The CIs for the difference in proportions between groups was computed using stratified Miettinen and Nurminen's (MN) confidence limits. This analysis was repeated for ORR based on the site investigator assessment. For each treatment arm, the overall visit response from the latest assessment prior to surgery was summarised by n (%) for each category (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD] and not evaluable [NE])*"[5]
- The EAG thanks the company for the clarification, and apologise for having missed the 95% CIs in Table 16 of the CS.[3]

3.2.5.5 OS

The CS[3] defines OS as the time from randomisation to death. The CS[3] reports that OS was not subject to a formal analysis at the interim cut-off date (10 November 2022). The rationale for this was that i) a longer period is required to collect OS data, and ii) that the measurement of OS may be "*confounded by the effects of subsequent therapies used in later lines following recurrence or progression*".

At the 10 November 2022 cut-off date, the CS[3] reports that, "*OS data had* [redacted] *with a HR of* [redacted]*. The median (range) of OS follow-up was* [redacted] *months in the perioperative durvalumab arm* [redacted] *and* [redacted] *months for the perioperative placebo arm (*[redacted]*).*" Figure 3.5 summarises these results.

Figure 3.5: KM plot of OS, mITT population at DCO 10 November 2022

Based on Figure 7, CS.[3]

Note: durvalumab + SoC and placebo + SoC refers to the perioperative durvalumab and the perioperative placebo arms in AEGEAN
CI = confidence interval; CS = company submission; DCO = data cut-off; HR = hazard ratio; KM = Kaplan-Meier; mITT = modified intention to treat; NC = not calculable; NR = not reached; OS = overall survival; SoC = standard of care

EAG comment:

- The rationale for the company not carrying out a full analysis appears weak. If the follow-up period is so short that the event rate is extremely low, then a full analysis would indeed appear inappropriate, but the proportion dying by the point of cut-off was 22%. This is far higher than the risk of pCR at the same DCO, which was subject to full analysis. Secondly, the fears of confounding by subsequent therapies are unfounded because there is no reason why the arms should differ in subsequent therapies given the double-blind nature of the study. Given the clear equipoise between arms in the 'immature' OS results, the failure to classify the result as a 'formal' result, without an adequate rationale, suggests bias. The company were asked[4] to explain more fully the reasons why OS was not subject to a 'formal' analysis.
- The company responded by stating that, "*The MTP uses a hierarchical, gatekeeping strategy that dictates the testing of OS. The MTP stipulates that OS will not be tested until a positive DFS result. Since DFS did not meet the prespecified boundary to declare statistical significance at EFS IA1, OS was not formally tested for statistical significance. The OS testing of the DCOs provided in the CS was performed on an ad-hoc basis to support regulatory procedures. Although this testing helps inform the benefit-risk assessment, it does not possess the statistical power of the MTP and therefore cannot be considered part of the formal testing procedure. The sponsor remains blinded to DFS (the gatekeeping outcome for OS), and the study continues in a blinded manner, with patients and investigators blinded as to treatment assignment.*"[5]
- The EAG thanks the company for this clarification, noting that the lack of a formal analysis of OS was consistent with the pre-hoc MTP plan.

The CS[3] then reports results from the safety analysis cut-off date at 120 days ([redacted]). This showed a HR of [redacted] (95% CI [redacted] to [redacted]). Figure 3.6 summarises this result.

Figure 3.6: KM of OS at D120SU

Based on Figure 8, CS[3].
Note: durvalumab + SoC and placebo + SoC refers to the perioperative durvalumab and the perioperative placebo arms in AEGEAN.
CI = confidence interval; CS = company submission; D120SU = day 120 safety update; DCO = data cut-off; KM = Kaplan-Meier; NC = not calculable; NR = not reached; OS = overall survival; SoC = standard of care

EAG comment:

- The only clinical outcome where the result at 120 days is reported appears to be the outcome that did not show significant differences at the primary or final analysis cut-off. The company were asked[4] to explain why the results at 120 days were not used for the other outcomes, and also why they thought it appropriate to deviate from the primary or final analysis results for this outcome.
- The company responded by stating that, "*The safety analysis was performed as part of the FDA regulatory procedure. This ad-hoc analysis was agreed with the FDA and was limited to safety outcomes and OS. The deviation from MTP for the OS outcome was specifically agreed with the regulatory body to support the benefit-risk assessment as not to delay patient access to treatment whilst further OS data are collected*."[5]
- In relation to the company's statement above, the EAG acknowledges that this approach was agreed with the FDA, but also notes that the 120-day data were, like the 10 November 2022 data, informal data. This is because the MTP would also designate the 120-day OS analysis as informal (as DFS had not yet been declared statistically significant). If neither the 10 November 2022 nor 120-day OS data were 'formal' analyses, they appear to have equal status. Therefore, the EAG does not understand why the more conservative data yielded at the 10 November 2022 DCO were not used as the solely presented analysis, to remain in line with the other outcomes. This remains a key issue.

3.2.5.6 HRQoL

HRQoL was assessed using EuroQoL 5-Dimension, 5-Level health status utility index (EQ-5D-5L) at DCO 10 November 2022. The CS[3] states that, "*Only data in the neoadjuvant period (Week 12) were evaluated at the time of the primary analysis of EFS to preserve the integrity of study blinding for the DFS analysis. The evaluation of HRQoL for the adjuvant period (for both the resected set and the modified resected set) is ongoing and will be analysed at the same time as the DFS analyses*."

The CS[3] reported that, "[redacted]"

EAG comment:

- The company has not reported in detail any of the HRQoL data in the CS[3] or appendices. This gives the impression that the company is downplaying the non-significant differences. Certainly, the lack of the data, with associated tables and figures, does tend to reduce attention to this outcome. The company were asked[4] to provide the data.
- The company responded by stating that, "*The company reported EQ-5D-5L results as these data were deemed the most relevant HRQoL data for this appraisal. Additional PRO/HRQoL data were collected as secondary and exploratory endpoints in the AEGEAN trial…."*[5]
- The company kindly provided these more complete data for the other quality of life (QoL) outcomes, summarised in Tables 3.13 to 3.16 below. These data demonstrate that there were no differences between placebo and durvalumab in terms of QoL changes. A relative increase in QoL would be expected from an effective and safe treatment, and so this is a key issue.

Table 3.13: Compliance with EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L by visit

Timepoint	Compliance	Perioperative durvalumab n=366	Perioperative placebo n=374
EORTC QLQ-C30			
Neoadjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
Neoadjuvant week 12	Expected forms Compliance rate (%)	[redacted]	[redacted]
Adjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
EORTC QLQ-LC13			
Neoadjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
Neoadjuvant week 12	Expected forms Compliance rate (%)	[redacted]	[redacted]
Adjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]

Timepoint	Compliance	Perioperative durvalumab n=366	Perioperative placebo n=374
EQ-5D-5L			
Neoadjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]
Neoadjuvant week 12	Expected forms Compliance rate (%)	[redacted]	[redacted]
Adjuvant baseline	Expected forms Compliance rate (%)	[redacted]	[redacted]

Based on Table 10, company response to clarification.[5]

*Adjuvant baseline is the latest measurement after surgery but before the first adjuvant dose

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (lung cancer); EQ-5D-5L = 5 level EuroQol

Table 3.14: EORTC QLQ-C30 global measure of health status/QoL

Timepoint	Measure	Perioperative durvalumab n=366	Perioperative placebo n=374
Change from neoadjuvant baseline			
Neoadjuvant baseline	n Absolute score, mean (SD)	[redacted]	[redacted]
Week 12	n Change from baseline, mean (SD)	[redacted]	[redacted]
Adjuvant baseline*	n Change from baseline, mean (SD)	[redacted]	[redacted]
Clinically relevant changes with respect to neoadjuvant baseline			
Week 12	n Worsened n (%) Improved n (%) Stable n (%)	[redacted]	[redacted]
Adjuvant baseline*	n Worsened n (%) Improved n (%) Stable n (%)	[redacted]	[redacted]

Based on Table 11, company response to clarification.[5]

*Adjuvant baseline is the latest measurement after surgery but before the first adjuvant dose

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SD = standard deviation

Table 3.15: EQ-5D-5L index and VAS scores change from baseline over time, with respect to neoadjuvant baseline (mITT)

EQ-5D-5L		Perioperative durvalumab n=366	Perioperative placebo n=374
EQ-5D-5L index score			
Baseline	n Absolute score mean (SD)	[redacted]0.8379 (0.15322)	[redacted]0.8379 (0.15326)
Week 12	n Change from baseline mean (SD)	[redacted]-0.0369 (0.18529)	[redacted]-0.0244 (0.22071)
Adjuvant baseline*	n Change from baseline mean (SD)	[redacted]-0.0677 (0.18183)	[redacted] -0.0623 (0.18373)
EQ-5D-5L VAS score			
Baseline	n Absolute score mean (SD)	[redacted]75.4 (15.89)	[redacted]74.2 (17.42)
Week 12	n Change from baseline mean (SD)	[redacted]-3.7 (19.01)	[redacted]-2.0 (18.15)
Adjuvant baseline*	n Change from baseline mean (SD)	[redacted]-4.9 (18.29)	[redacted]-5.0 (18.39)

Based on Table 12, company response to clarification.[5]

*Adjuvant baseline is the latest measurement after surgery but before the 1st adjuvant dose

EQ-5D-5L = 5 level EuroQol; mITT = modified intention-to-treat; SD = standard deviation; VAS = visual analogue scale

3.2.5.7 Sub-grouping

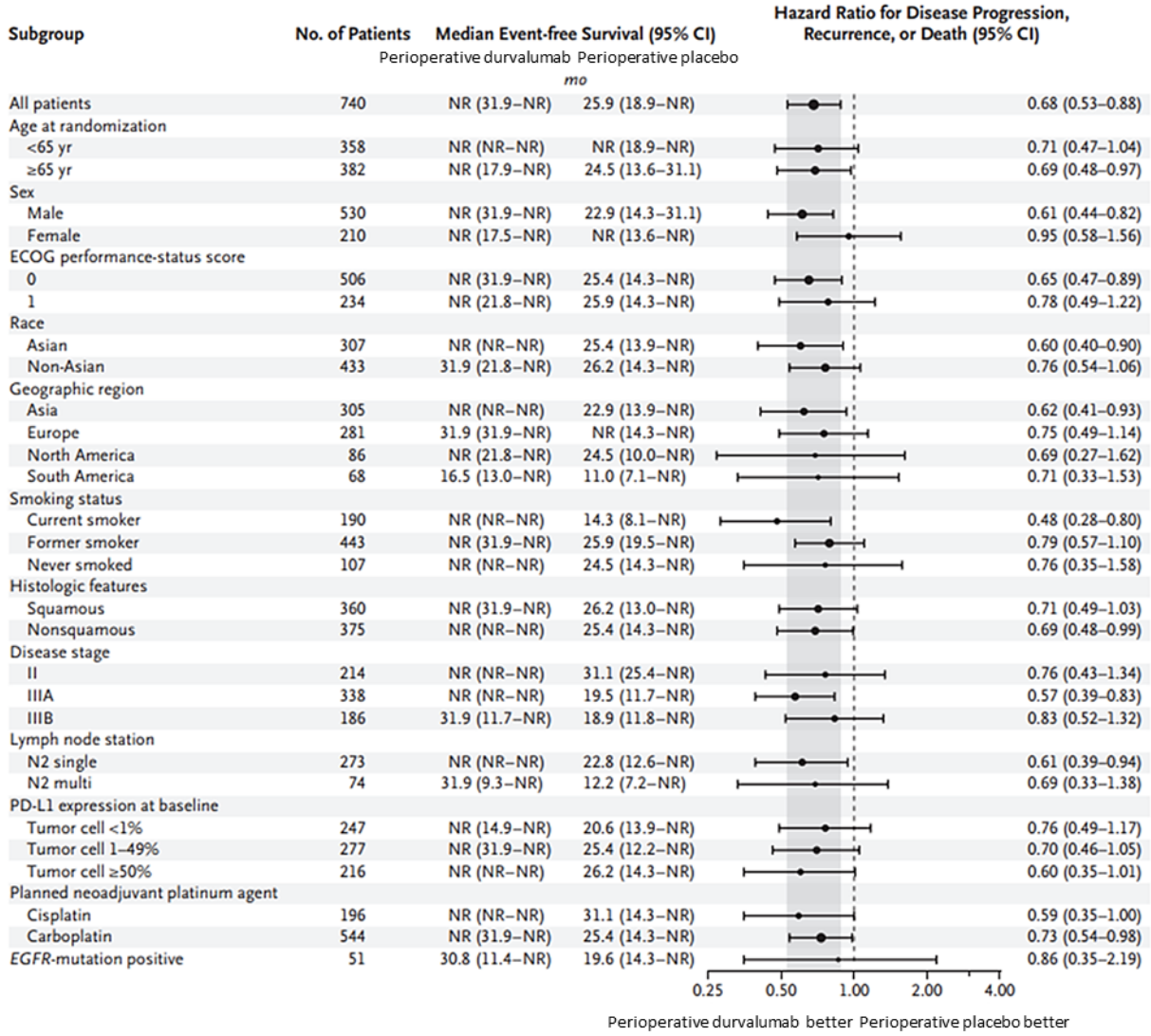
Prespecified subgroup analyses were performed for EFS and pCR.

3.2.5.7.1 EFS

At the primary analysis of EFS with DCO on 10 November 2022, subgroup analyses for age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), race, geographic region, smoking history, histology, disease stage, lymph node station, PD-L1 expression, and planned neoadjuvant platinum agent were performed (Figure 3.7).

Sex or smoking status appeared to make an appreciable difference to the point estimate.

Figure 3.7: Subgroup analyses of EFS (BICR using RECIST 1.1), mITT population



Based on Figure 11, CS[3] DCO 10 November 2022 (N=740).

The 95% CIs were estimated using a stratified Miettinen and Nurminen method for all patients (mITT) and an unstratified Miettinen and Nurminen method for subgroups. The size of the data point is proportional to the number of patients for each subgroup, and the horizontal bars represent the 95% CIs. Shading indicates the HR and 95% CI for EFS in the mITT population.

*Race was self-reported per electronic case report form.

[†]Determined using the Ventana SP263 immunohistochemistry assay.

BICR = Blinded Independent Central Review; CI = confidence interval; CS = company submission DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EGFR = epidermal growth factor receptor; HR = hazard ratio; mITT = modified intention-to-treat; NR = not reached; PD-L1 = programmed cell death ligand-1; RECIST = Response Evaluation Criteria in Solid Tumours

EAG comment:

- The company has carried out a thorough sub-group analysis, selecting appropriate variables pre-hoc. The company is correct to assert that the analyses lack statistical power, which is probably why statistical analyses for differences between strata have not been attempted. In any event, there would be a risk of type II errors (where real differences might remain undetected

because of the lack of statistical power) even if a formal statistical analysis had been carried out. Therefore, because detection of sub-group differences is important, there is a need to look for possible effects without the help of statistical testing. The possible effects for gender and smoking status appear potentially important because if these characteristics do influence the EFS effect, then any differences in the proportions of men and women, or smokers and non-/ex-smokers between the trial and the United Kingdom (UK) target population could affect the representativeness of the EFS effects in the trial and the UK target population. The company were asked[4] for the characteristics of the UK target population, including these two characteristics, so that any possible effects on external validity of trial findings can be evaluated.

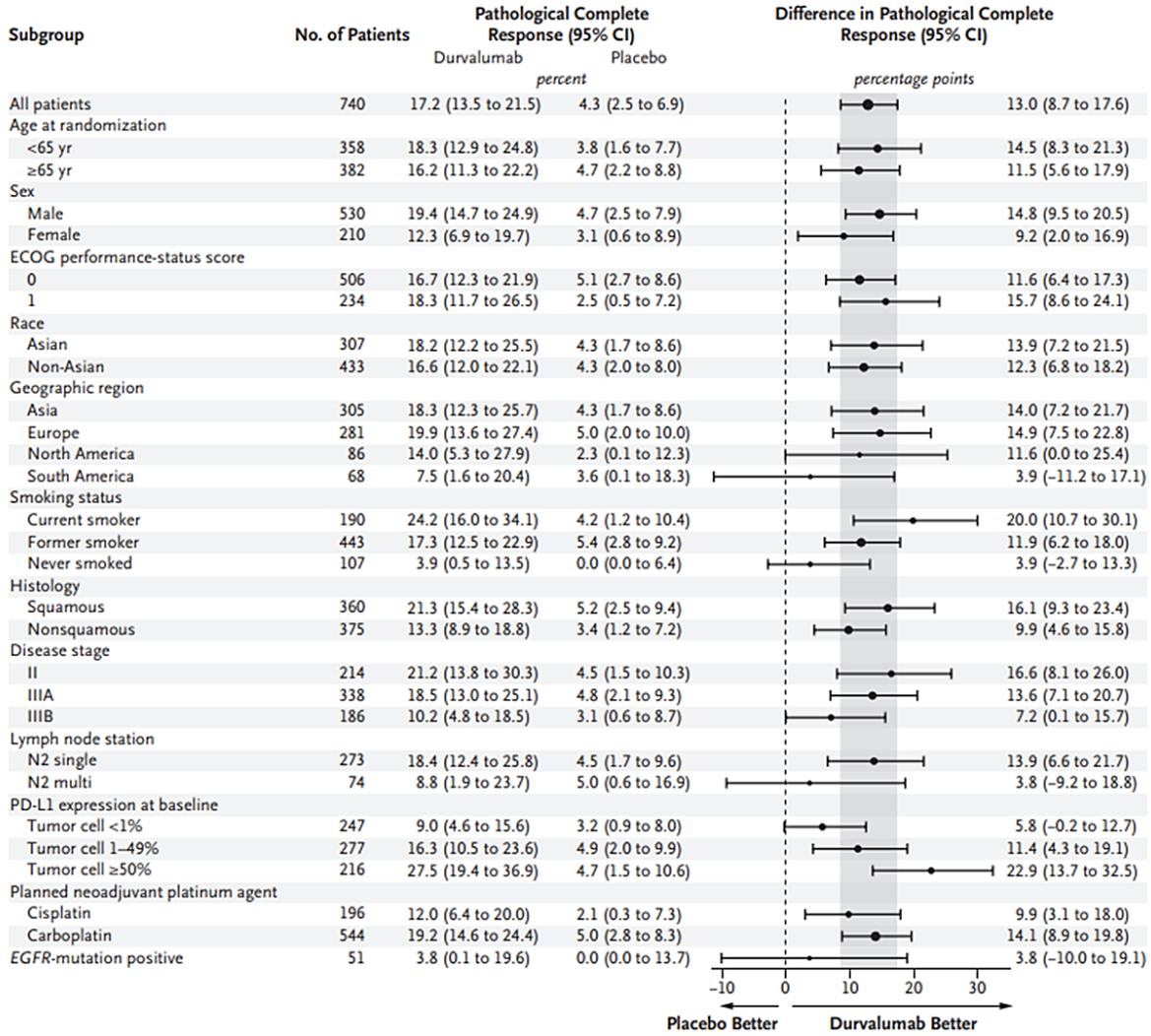
- The company responded by stating that, "*The UK target population is aligned with the expected license for perioperative durvalumab: adults with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements. Clinicians at the advisory board held in January 2024 confirmed that the AEGEAN trial was generalisable to the UK patient population. Some minor differences in the percent of males, those with N2 disease and the percent of patients with squamous histology compared to what is seen in clinical practice were noted, but these differences were not seen as a concern to generalisability. For further detail on the generalisability of the AEGEAN trial population to the UK, an advisory board report including a comprehensive summary and analysis of discussions and recommendations made by the UK clinical experts has been provided to the EAG.*"[5]
- In response to the company's statement above, the EAG do not think that clinical expert opinion is adequate for deciding upon trial and target population similarity. In the absence of objective data, the EAG considers that threats to the external validity of the trial cannot be excluded, and so assumptions about the generalisability of trial findings to the UK target population are compromised. For example, without access to data on the characteristics of the UK target population, it is not possible for the EAG to confirm the clinical experts' view that differences between populations in gender were not a threat to generalisability, particularly given that the sub-group analyses suggested that gender might be an effect modifier. The reference for the Advisory Board report [company reference 29: The 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.] was not available in the list of references provided by the company. This remains a key issue.

3.2.5.7.2 pCR

At the final analysis of DCO on 10 November 2022, subgroup analyses for age, sex, ECOG PS, race, geographic region, smoking history, histology, disease stage, lymph node station, PD-L1 expression, planned neoadjuvant platinum agent, and EGFR mutation status were performed (Figure 3.8).

PD-L1 expression, lymph node station, disease stage, smoking status and geographic region all appeared to be important effect modifiers.

Figure 3.8: Subgroup analysis of pCR, mITT population



Based on Figure 12, CS[3]
DCO 10 November 2022
The 95% CIs were estimated using a stratified Miettinen and Nurminen method for all patients (mITT) and an unstratified Miettinen and Nurminen method for subgroups. The size of the data points is proportional to the number of patients for each subgroup, and the horizontal bars represent the 95% CIs. Shading indicates the HR and 95% CI for pCR in the mITT population.
*Race was self-reported per electronic case report form
†Determined using the Ventana SP263 immunohistochemistry assay
BICR = Blinded Independent Central Review; CI = confidence interval; CS = company submission; DCO = data cut-off; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; mITT = modified intention-to-treat; NR = not reached; pCR = pathological complete response; PD-L1 = programmed cell death ligand-1

EAG comment:

- The company has carried out a thorough sub-group analysis, selecting appropriate variables pre-hoc. The company is correct to assert that the analyses lack statistical power, which is probably why statistical analyses for differences between strata have not been attempted. In any event, there would be a risk of type II errors (where real differences might remain undetected

because of the lack of statistical power) even if a formal statistical analysis had been carried out. Therefore, because detection of sub-group differences is important, there is a need to look for possible effects without the help of statistical testing. The possible effects for PD-L1 expression, lymph node station, disease stage, smoking status and geographic region appear potentially important because if these characteristics do influence the pCR effect, then any differences in the proportions of these characteristics between the trial and the UK target population could affect the representativeness of the pCR effects in the trial and the UK target population. The company were asked[4] for the characteristics of the UK target population, including PD-L1 expression, lymph node station, disease stage, smoking status and geographic region, so that any possible effects on external validity of trial findings can be evaluated.

- The company responded by stating that, "*The UK target population is aligned with the expected license for perioperative durvalumab: adults with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements. Clinicians at the advisory board held in January 2024 confirmed that the AEGEAN trial was generalisable to the UK patient population. Some minor differences in the percent of males, those with N2 disease and the percent of patients with squamous histology compared to what is seen in clinical practice were noted, but these differences were not seen as a concern to generalisability. For further detail on the generalisability of the AEGEAN trial population to the UK, an advisory board report including a comprehensive summary and analysis of discussions and recommendations made by the UK clinical experts has been provided to the EAG*"[5]
- The EAG do not think that clinical expert opinion is adequate for the important issue of trial and target population similarity. In the absence of objective data, the EAG considers that threats to the external validity of the trial cannot be excluded, and so assumptions about the generalisability of trial findings to the UK target population are compromised. The reference for the Advisory Board report [company reference 29: The 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.] was not available in the list of references provided by the company. This remains a key issue.

3.2.6 Adverse effects in the included trials

The evaluation of AEs is based on the 799 participants in the safety analysis population at DCO 10 November 2022. The post-surgical AE assessment is based on the participants in the modified safety analysis population who underwent surgery (n=597).

Table 3.16 presents a summary of any grade AEs reported in the safety analysis population. The CS[3] states that "*Deaths that occurred in each arm were not considered to be related to study treatment in most cases. Immune-mediated AEs of any grade were reported in 23.7% of patients in the perioperative durvalumab arm and 9.3% of patients in the perioperative placebo arm. Most were grade 1 or 2 adverse events, with grade 3 or 4 immune-mediated AEs reported in 4.2% and 2.5%, respectively, in the two arms. Treatment discontinuations were higher in the perioperative durvalumab arm compared to the perioperative placebo arm in the neoadjuvant period, due to discontinuations resulting from two active agents (durvalumab and PDC)*"

Table 3.16: Summary of any grade AEs in AEGEAN in the overall study period, safety analysis set

Overall study period	Perioperative durvalumab (n=401)	Perioperative placebo (n=398)
AEs of any grade and any cause, n (%)	**387 (96.5)**	**377 (94.7)**
Maximum grade 3 or 4	170 (42.4)	172 (43.2)
SAEs	151 (37.7)	125 (31.4)
Events leading to death	23 (5.7)	15 (3.8)
Leading to discontinuation of durvalumab or placebo	48 (12.0)	24 (6.0)
Leading to cancellation of surgery	7 (1.7)	4 (1.0)
AEs of any grade possibly related to durvalumab, placebo or chemotherapy, n (%)	**348 (86.8)**	**321 (80.7)**
Maximum grade 3 or 4	130 (32.4)	131 (32.9)
Events leading to death[b]	7 (1.7)	2 (0.5)
Any immune-related AE	**95 (23.7)**	**37 (9.3)**
Any grade 3 or 4	17 (4.2)	10 (2.5)

Based on Table 24, CS[3]
DCO 10 November 2022 (n=799)
[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

The most common AEs are reported in Table 3.17.

Table 3.17: Summary of most common AEs in AEGEAN (overall study period), safety analysis set[a]

AEs, n (%)	Perioperative durvalumab (n=401)		Perioperative placebo (n=398)	
	Any grade	Maximum Grade 3 or 4	Any grade	Maximum Grade 3 or 4
Anaemia	136 (33.9)	26 (6.5)	126 (31.7)	26 (6.5)
Nausea	101 (25.2)	1 (0.2)	115 (28.9)	1 (0.3)
Constipation	100 (24.9)	1 (0.2)	84 (21.1)	0
Decreased appetite[b]	73 (18.2)	1 (0.2)	70 (17.6)	1 (0.3)
Alopecia	69 (17.2)	0	63 (15.8)	1 (0.3)
Neutropenia	68 (17.0)	36 (9.0)	71 (17.8)	38 (9.5)

AEs, n (%)	Perioperative durvalumab (n=401)		Perioperative placebo (n=398)	
	Any grade	Maximum Grade 3 or 4	Any grade	Maximum Grade 3 or 4
Neutrophil count decreased	64 (16.0)	39 (9.7)	57 (14.3)	43 (10.8)
Rash	56 (14.0)	2 (0.5)	34 (8.5)	1 (0.3)
Diarrhoea	52 (13.0)	3 (0.7)	49 (12.3)	3 (0.8)
Fatigue	52 (13.0)	0	46 (11.6)	1 (0.3)
Asthenia	50 (12.5)	0	54 (13.6)	5 (1.3)
Pruritus	47 (11.7)	1 (0.2)	22 (5.5)	0
Vomiting	45 (11.2)	3 (0.7)	42 (10.6)	4 (1.0)
COVID-19[c]	45 (11.2)	1 (0.2)	35 (8.8)	3 (0.8)
Procedural pain	44 (11.0)	1 (0.2)	48 (12.1)	2 (0.5)
Insomnia	41 (10.2)	0	46 (11.6)	0

Based on Table 25, CS.[3]

DCO 10 November 2022 (n=799)

[a]The safety analysis set includes all randomised patients who received at least one dose of study treatment; one patient assigned to the perioperative placebo arm erroneously received a single cycle of durvalumab (in the adjuvant phase) and was included in the perioperative durvalumab arm for the safety analysis set; AEs were graded using CTCAE version 5.0. Included are AEs reported with an any-grade incidence of at least 10% in the perioperative durvalumab arm during the overall study period, which spans from the first dose of study treatment (durvalumab or placebo or chemotherapy) until the earliest of: the last dose of study treatment or surgery + 90 days (taking the latest dose of durvalumab or placebo or chemotherapy or the date of surgery, + 90 days); the DCO date; or the date of the first dose of subsequent anti-cancer treatment.

[b]Two patients (one in each arm) had decreased appetite with an outcome of death (maximum grade 5); the fatal event in the perioperative durvalumab arm was assessed as possibly related to study treatment by the investigator.

[c]Six patients had COVID-19 events of maximum grade 5 (perioperative durvalumab arm, n=5; perioperative placebo arm, n=1); all COVID-19 deaths were assessed by the investigator as unrelated to study treatment (note: COVID-19 is summarised as a grouped term comprising the 'COVID-19' and 'COVID-19 pneumonia' AE preferred terms).

AE = adverse events; COVID-19 = coronavirus disease 2019; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; DCO =data cut-off

Any grade AEs possibly related to surgery, or with any surgical complication are given in Table 3.18.

Table 3.18: Summary of AEs possibly related to surgery and surgical complications in AEGEAN (post-surgery period), underwent surgery, modified safety analysis set

Post-surgery period[a]	Perioperative durvalumab (N=296)	Perioperative placebo (N=301)
Any grade AEs possibly related to surgery, n (%)[b]	**119 (40.2)**	**118 (39.2)**
Maximum grade 3 or 4	25 (8.4)	28 (9.3)
SAEs	33 (11.1)	33 (11.0)
Outcome of death[c]	6 (2.0)	4 (1.3)

Post-surgery period[a]	Perioperative durvalumab (N=296)	Perioperative placebo (N=301)
Patients with any surgical complication, n (%)[d]	**175 (59.1)**	**181 (60.1)**
Maximum reported by Claven-Dindo classification grade		
1	125 (42.2)	131 (43.5)
2	32 (10.8)	25 (8.3)
≥3	18 (6.1)	25 (8.3)

Based on Table 26, CS[3]
DCO 10 November 2022
[a] This includes AEs between the date of surgery (including the date of surgery) and the earliest of the date of surgery + 90 days or first dose of subsequent anti-cancer therapy; this also includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.
[b] The summary of AEs possibly related to surgery and surgical complications summary reflect data collected for all patients in the modified safety analysis set who underwent surgery (including one patient assigned to the perioperative placebo arm who erroneously received a single cycle of durvalumab and was therefore included in the perioperative durvalumab arm for safety assessment), with AEs graded using the National Cancer Institute Common Toxicity Criteria for AEs, version 5.0.
[c] There were no AEs with outcome of death, possible related to surgery, within 1 day of surgery in either arm. Note: All deaths regardless of any causality within 30 days of surgery = 12 (perioperative durvalumab arm, n=4; perioperative placebo arm, n=8)
[d] Included infectious pleural effusion (perioperative placebo arm, n=1), pneumonia (perioperative durvalumab arm, n=2; perioperative placebo arm, n=1) septic shock (perioperative durvalumab arm, n=1), acute respiratory failure (perioperative placebo arm, n=1), bronchopleural fistula (perioperative durvalumab arm, n=1), interstitial lung disease (perioperative durvalumab arm, n=1), pneumonitis (perioperative durvalumab arm, n=1), pulmonary haemorrhage (perioperative placebo arm, n=1), and post-procedural pulmonary embolism (perioperative durvalumab arm, n=1)
AE = adverse events; CS = company submission; DCO = data cut-off; SAEs = serious adverse events

A summary of AEs possibly related to a study treatment (durvalumab, platinum-doublet chemotherapy (PDC), or placebo) and discontinuations as the day 120 safety update (D120SU) are presented in Tables 3.19 and 3.20, respectively.

Table 3.19: Summary of AEs possibly related to treatment or surgery at D120SU

AE category (overall period[a])	Number (%) of patients[b]	
	Perioperative durvalumab (N = 401)	Perioperative placebo (N = 398)
Any AE	[redacted]	[redacted]
Possibly related to any study treatment[c]	[redacted]	[redacted]
Possibly related to durvalumab/placebo[c]	[redacted]	[redacted]
Possibly related to PDC (at least one component)[c]	[redacted]	[redacted]
Possibly related to surgery[c]	[redacted]	[redacted]
Possibly related to PORT[c]	[redacted]	[redacted]
Any AE of maximum CTCAE grade 3 or 4 [d]	[redacted]	[redacted]
Possibly related to any study treatment[c, d]	[redacted]	[redacted]

AE category (overall period[a])	Number (%) of patients[b]	
	Perioperative durvalumab (N = 401)	Perioperative placebo (N = 398)
Possibly related to durvalumab/placebo[c, d]	[redacted]	[redacted]
Possibly related to PDC (at least one component)[c, d]	[redacted]	[redacted]
Possibly related to surgery[c, d]	[redacted]	[redacted]
Possibly related to PORT[c, d]	[redacted]	[redacted]
Any AE with outcome of death	[redacted]	[redacted]
Possibly related to any study treatment[c]	[redacted]	[redacted]
Possibly related to durvalumab/placebo[c]	[redacted]	[redacted]
Possibly related to PDC (at least one component)[c]	[redacted]	[redacted]
Possibly related to surgery[c]	[redacted]	[redacted]
Possibly related to PORT[c]	[redacted]	[redacted]

Based on Table 27, CS[3]

[redacted]

Study treatment includes durvalumab/placebo/SoC and excludes surgery/PORT. AEs collected between first dose and the earliest of: maximum date of (last dose or surgery) +90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

[a] Overall period refers to the neoadjuvant period, post-surgery and adjuvant period.

[b] Patients with multiple events in the same category are counted only once in that category.

[c] As assessed by the investigator. Missing responses are counted as possibly related. Study treatment includes durvalumab, PDC, placebo, in this context surgery is not included as a study treatment.

[d] Maximum CTCAE grade per patient/treatment period/event is considered.

AE = adverse event; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; D120SU = day 120 safety update; PDC = platinum-doublet chemotherapy; PORT = post-operative radiotherapy; SoC = standard of care

Table 3.20: Summary of discontinuations at D120SU

	Perioperative durvalumab (N=401)	Perioperative placebo (N=398)
Any AE leading to discontinuation of any study treatment	[redacted]	[redacted]
Leading to discontinuation of durvalumab/placebo	[redacted]	[redacted]
Possibly related to durvalumab/placebo leading to discontinuation of durvalumab/placebo[c]	[redacted]	[redacted]
Leading to discontinuation of two chemotherapy agents	[redacted]	[redacted]
Leading to discontinuation of PDC (at least one component), possibly related to PDC (at least one component)[c]	[redacted]	[redacted]
Any SAE (including events with outcome of death)[e]	[redacted]	[redacted]
Possibly related to any study treatment[c, e]	[redacted]	[redacted]
Possibly related to durvalumab/placebo[c, e]	[redacted]	[redacted]
Possibly related to PDC (at least one component)[c, e]	[redacted]	[redacted]
Possibly related to surgery[c, e]	[redacted]	[redacted]

	Perioperative durvalumab (N=401)	Perioperative placebo (N=398)
Possibly related to PORT[c, e]	[redacted]	[redacted]
Any imAE[f]	[redacted]	[redacted]
Infusion related reaction[g]	[redacted]	[redacted]

Based on Table 28, CS[3]
[redacted]

Study treatment includes durvalumab/placebo/SoC and excludes surgery/PORT. AEs collected between first dose and the earliest of: maximum date of (last dose or surgery) +90 days, date of first dose of subsequent anti-cancer therapy. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period.

[a] Overall period refers to the neoadjuvant period, post-surgery and adjuvant period, i.e., neoadjuvant durvalumab + PDC followed by surgery and durvalumab monotherapy, and neoadjuvant placebo + PDC followed by surgery and placebo.

[b] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[c] As assessed by the investigator. Missing responses are counted as possibly related. Study treatment includes durvalumab, PDC, placebo, in this context surgery is not included as a study treatment.

[d] Maximum CTCAE grade per patient/treatment period/event is considered.

[e] Seriousness, as assessed by the investigator. An AE with missing seriousness is considered serious.

[f] AEs adjudicated as imAEs.

[g] Patients with AEs of special interest of infusion related reaction.

AE = adverse event; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; D120SU = day 120 safety update; imAE = immune-mediated adverse event; PDC = platinum-doublet chemotherapy; PORT = post-operative radiotherapy; SAE = serious adverse event; SoC = standard of care

EAG comment: The company's assertion that "*perioperative durvalumab + neoadjuvant PDC was well-tolerated with manageable adverse events*"[3] is upheld to a large extent by these results. However, the greater risk of 'deaths possibly related to any study treatment' in perioperative durvalumab compared to perioperative placebo has a relative risk of large magnitude, at 3.47 (95% CI: 0.73, 16.62). The 95% CIs suggest this result may be explained by sampling error, but because of the importance of the adverse outcome it would probably be prudent to consider the possibility that it represents a real population effect. The absolute risk difference of 0.01 (-0.00, 0.03) for this outcome implies, given a real population effect, that one in every 100 people with resectable NSCLC that are given perioperative durvalumab instead of perioperative placebo may die because of the treatment given, rather than because of the disease process or any other reason. The clinical significance of these adverse results, albeit uncertain, should therefore be weighed up against the benefits by the committee. It should be noted that the AEGEAN statistical analysis plan did not include formal statistical testing for AE results.

3.2.7 Ongoing studies

The CS[3] reports that, "*The AEGEAN study is currently ongoing and has an estimated completion date of September 2028. Additional analyses for EFS are scheduled at approximately 40% (second interim analysis) and 50% (final analysis) data maturity. Disease-free survival will be tested at the second interim analysis of EFS and in the meantime, AEGEAN remains blinded. Per the MTP, OS will be tested when a significant result for DFS is reached in subsequent analyses*".

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Because the AEGEAN study compared perioperative durvalumab to perioperative placebo, rather than any of the decision problem comparators, ITCs were required to estimate the effects of perioperative durvalumab to the decision problem comparators. The CS[3] states that two ITCs were conducted:

1. An anchored matching adjusted indirect comparison (MAIC) comparing perioperative durvalumab with neoadjuvant nivolumab + PDC.
2. A NMA to compare perioperative durvalumab against i) adjuvant PDC and ii) surgery alone.

3.3.1 MAIC

The trials selected for the MAIC from the SLR were AEGEAN (perioperative durvalumab) and CheckMate 816 (neoadjuvant nivolumab + PDC). No other trials were eligible, as no other trials evaluated perioperative durvalumab or neoadjuvant nivolumab + PDC. The AEGEAN trial has been described in Section 3.2, so only CheckMate 816 will be discussed in this Section.

CheckMate 816 was a randomised trial that evaluated neoadjuvant nivolumab + PDC versus neoadjuvant PDC alone. Reference to the research paper for this study shows that CheckMate 816 patients were adults with resectable stage IIB to IIA NSCLC, an ECOG PS of 0 or 1, and no previous therapy.[16] Patients with known ALK translocations or EGFR mutations were excluded. The CS[3] reports that differences existed between AEGEAN and CheckMate 816 in terms of disease stage, PD-L1 expression, region and percentage of cisplatin use.

EAG comment:

- Although patient and carer blinding were not mentioned in the CheckMate 816 study report, it is likely that it would not have been possible to blind patients or care givers.[16] The nivolumab + PDC group would have had two different treatments but the comparator PDC arm, without a placebo treatment, would have had only the single PDC treatment. Therefore, the group allocation would be clear to patients and care providers. This is not a concern to the EAG, as it would probably have a conservative effect on the overall MAIC result. This is because a spurious improvement in the effect size for neoadjuvant nivolumab + PDC would reduce the estimated effect size between perioperative durvalumab and neoadjuvant nivolumab + PDC.
- The differences between trials in terms of population characteristics are not ideal, as these threaten the principle of transitivity (we cannot assume that (using an outcome expressed as in odds ratio (OR)) logit (B versus A) - logit (C versus A) = logit (B versus C) if B versus A and A versus C are carried out in different populations), but theoretically this can be amenable to the MAIC procedure, where adjustment of one of the datasets is made to increase comparability. Please see Section 3.4.1 below for details of the MAIC procedure.

3.3.2 NMA

To evaluate the effectiveness of perioperative durvalumab versus the remaining two comparators in the decision problem (adjuvant PDC, and active monitoring) an NMA was set up, rather than conducting two pairwise MAICs. The company justifies this as follows: "*This approach was taken to include evidence from the multiple studies identified in the SLR and in the absence of clear candidates amongst*

these trials for conducting pairwise MAICs".[3] It should be noted that the company took surgery as a proxy for active monitoring (please see Section 2.3 for more discussion on this topic).

The treatments included in the NMA were perioperative durvalumab + neoadjuvant PDC, adjuvant PDC, neoadjuvant PDC and surgery alone (as a proxy for active monitoring). These involved the following seven phase III RCTs: AEGEAN; NATCH; Rosell et al. 1994; CHEST; MRC LU22/NVALT2/EORTC0812; SWOGS9900; Li et al. 2009. Risk of bias was generally high, with a common feature being a lack of information on allocation concealment. More information can be found in the CS appendices Table 13.[10]

A summary of the population and treatments in these trials are given in Tables 3.21 and 3.22 below. Further detail on the treatments included in the NMA can be viewed in Tables 21 to 24 of the CS Appendix.[10]

Table 3.21: Overview of the mITT population NMA: sample size and number of events (overall and piecewise)

Study	Treatment	Total subjects	Subjects with events	Subjects with event within 3 months	Subjects with event after 3 months
AEGEAN[14]	Perioperative durvalumab	366	98 (26.8%)	18 (4.9%)	80 (21.9%)
	Neoadjuvant PDC	374	138 (36.9%)	20 (5.3%)	118 (31.6%)
CHEST[17]	Neoadjuvant PDC	129	65 (50.4%)	11 (8.5%)	54 (41.9%)
	Surgery alone	141	82 (58.2%)	15 (10.6%)	67 (47.5%)
Li 2009[18]	Neoadjuvant PDC	28	19 (67.9%)	0 (0.0%)	19 (67.9%)
	Surgery alone	28	24 (85.7%)	0 (0.0%)	24 (85.7%)
MRC LU/22/NVALT 2/EORTC 09012[19]	Neoadjuvant PDC	258	145 (56.2%)	28 (10.9%)	117 (45.3%)
	Surgery alone	261	153 (58.6%)	35 (13.4%)	118 (45.2%)
NATCH[20]	Adjuvant PDC	210	124 (59.0%)	37 (17.6%)	87 (41.4%)
	Neoadjuvant PDC	199	120 (60.3%)	15 (7.5%)	105 (52.8%)
	Surgery alone	210	133 (63.3%)	30 (14.3%)	103 (49.0%)
Rosell 1994[21, 22]	Neoadjuvant PDC	30	20 (66.7%)	1 (3.3%)	19 (63.3%)
	Surgery alone	30	30 (100.0%)	8 (26.7%)	22 (73.3%)
SWOG S9900[23]	Neoadjuvant PDC	169	109 (64.5%)	20 (11.8%)	89 (52.7%)
	Surgery alone	168	168 (100.0%)	17 (10.1%)	151 (89.9%)

Based on Table 40, CS Appendix D[10]

The number at risk and the number of events in comparator trials were based on pseudo patient-level data generated from digitisation of the EFS KM curves. Further details on how the piecewise data were derived for each time interval have been described previously.

CS = company submission; EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat; NMA = network meta-analysis; PDC = platinum-doublet chemotherapy

Table 3.22: Summary of population and treatment characteristics

Study of interest	Population/patient characteristics		Treatment characteristics		Comments and ITC feasibility recommendations
Neoadjuvant PDC versus adjuvant PDC versus surgery					
NATCH[20]	Includes stage I patients, with majority stage I Higher % male (87.9%)		3G chemotherapy – similar to AEGEAN		'Historical' studies with possible differences in design and outcomes compared with AEGEAN. Only NATCH provides evidence for EFS with adjuvant PDC – *include in network with surgery alone, which also includes direct evidence from NATCH.* Limited options to account for differences in disease stage e.g., via population-adjusted ITC or subgroup ITCs. No single study matches AEGEAN eligibility criteria according to stage or has similar baseline stage compared with AEGEAN. Regarding studies which include stage I/IB patients: NATCH reports subgroup EFS excluding stage I, but this only includes stage II T3 N1; across other studies, % stage IB is non-negligible and % stage III is considerably lower versus AEGEAN. Regarding studies which include stage IIIA only: subgroup ITC is an option, but several limitations due to other differences e.g., 2G chemotherapy; Asia only. Despite differences in stage and other factors, ITC with network including adjuvant PDC and surgery will be considered (with limitations noted), which include all relevant studies.
Neoadjuvant PDC versus surgery					
Rosell 1994[21 22]	Includes stage III only Higher % male (>90%)	Across all studies: Some variation in histology. No PD-L1 expression reported, and limited smoking status reported	2G chemotherapy	Across all studies: With exception of 2G versus 3G chemotherapy, assume type of chemotherapy and number of cycles (2-3 versus 4) received does not impact treatment effect for neoadjuvant PDC versus nCRT	
CHEST[17]	Includes stage IB patients, with majority stage IB		3G chemotherapy – similar to AEGEAN		
MRC LU22/NVALT 2/EORTC 08012[19]	Includes stage IB patients, with non-negligible % stage IB		Mixture of 2G/3G chemotherapy		
SWOG S9900[23]	Includes stage IB patients, with majority stage IB/II		3G chemotherapy – similar to AEGEAN		
Li 2009[18]	Includes stage IIIA only Asia only		3G chemotherapy – similar to AEGEAN		

Study of interest	Population/patient characteristics		Treatment characteristics		Comments and ITC feasibility recommendations
					As part of sensitivity analyses: Exclude studies with 2G chemotherapy Exclude studies with stage III Exclude Asia only, given that region (Asia versus non-Asia) is considered a potential TEM

Based on adapted from Table 28, CS Appendices[10]

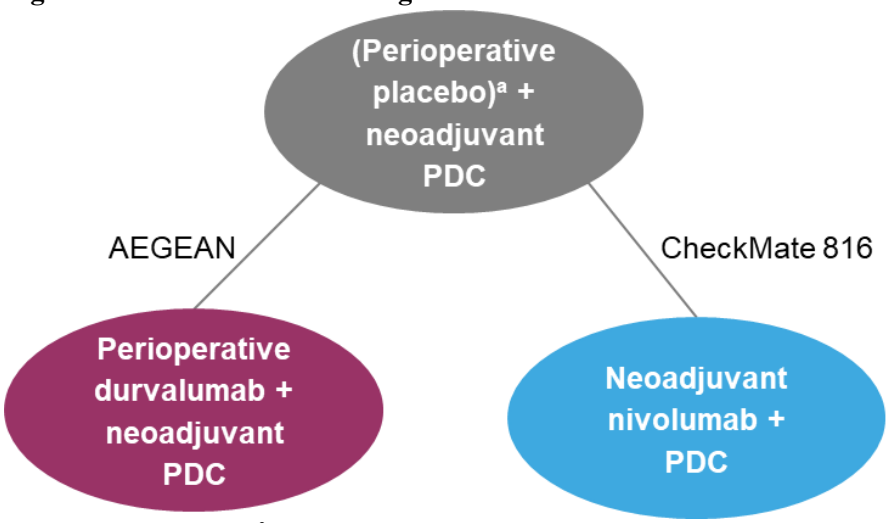
% = percentage; 2G = second generation; 3G = third generation; ALK = anaplastic lymphoma kinase; CS = company submission; EFS = event-free survival; EGFR = epidermal growth factor receptor; ITC = indirect treatment comparison; nCRT = neoadjuvant chemoradiotherapy; PDC = platinum-doublet chemotherapy; PD-L1 = programmed cell death ligand-1

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 MAIC

An anchored MAIC analysis was performed to compare the efficacy of perioperative durvalumab from AEGEAN with neoadjuvant nivolumab + PDC from CheckMate 816, utilising the common comparator arm of neoadjuvant PDC (with or without perioperative placebo) in both studies. Figure 3.9 shows the network of evidence utilised.

Figure 3.9: Anchored PAIC diagram for AEGEAN versus CheckMate 816



Based on Figure 13, CS[3]

[a] There is no placebo in CheckMate 816

CS = company submission; PAIC = population-adjusted indirect comparison; PDC = platinum-doublet chemotherapy

The base-case analysis for the MAIC included all possible effect modifiers in the propensity score weighting, regardless of whether these were imbalanced or not (i.e. disease stage (IIIB versus other; IIIA versus other), PD-L1 expression (<50% versus ≥50%; <1% versus ≥1%), histology, region (Asia versus non-Asia), sex, smoking status, and planned platinum chemotherapy were included as variables for weighting in the base-case analysis). Additionally, a scenario analysis was conducted to explore the impact on results of only weighting for those characteristics that were imbalanced between trials (i.e. disease stage, PD-L1 expression, region, and planned platinum chemotherapy included in the weighting).

After weighting, the baseline characteristics in AEGEAN matched those in CheckMate 816 for those variables that were included in the weighting. In the additional scenario, weighting resulted in an increase in the proportion of patients with non-squamous histology and the proportion of patients who had never smoked, introducing imbalances between AEGEAN and CheckMate 816 in these baseline characteristics, both of which are considered possible effect modifiers.

For the overall trial period base-case analysis, after weighting AEGEAN to match the CheckMate 816 population, [redacted] (Table 3.23). [redacted] estimated in scenario 1.

Table 3.23: MAIC EFS HRs for perioperative durvalumab versus neoadjuvant nivolumab + PDC (unweighted and after weighting in the base-case and scenario 1)

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]

Based on Table 20, CS[3]

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.

CS = company submission; DSU = Decision Support Unit; EFS = event-free survival; HR = hazard ratio; LCL = lower confidence limit; MAIC = matching adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed cell death ligand-1; PDC = platinum-doublet chemotherapy; TSD = Technical Support Document; UCL = upper confidence limit

The results of the piecewise analyses (stratification for follow-up periods of 0-3 months and >3 months) are shown in Table 3.24. The robustness of the piecewise MAIC results for the 0-3-month time interval is limited by a low number of events occurring in each trial across treatment arms [redacted]) in this time period.

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 [redacted].

Table 3.24: 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 1)

Comparison	Scenario	0–3 m time interval			3+ m time interval		
		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]

Based on Table 21, CS[3]

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

CS = company submission; DSU = Decision Support Unit; 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; TSD = Technical Support Document; UCL = upper confidence limit

EAG comment:

- In an anchored MAIC, it is important that the common treatment that anchors the analysis (in this case the comparator treatment in each of the two trials) is the same across the two trials. If it is not, then the transitivity assumption that (using an outcome expressed as in OR) logit (B versus A) - logit (A versus C) = logit (B versus C) (where B and C are the treatments of interest,

and A is the common comparator) is no longer tenable. It is not clear that the comparators were the same in this MAIC. The comparator in the AEGEAN trial was neoadjuvant placebo + PDC and adjuvant placebo, whereas in the CheckMate 816 trial the comparator was neoadjuvant PDC, apparently without placebo, and with no placebo given post-op. This constitutes quite a difference, because without placebo the comparator in the CheckMate 816 arm may yield less overall efficacy than otherwise. This will inevitably affect the indirect estimate. The company were asked[4] to consider this point and to estimate the effects this may have had on the indirect estimate of the EFS outcome.

- The company responded by stating that, "*Neoadjuvant nivolumab is considered a relevant comparator for this appraisal thus a comparison versus perioperative durvalumab was required. As described in Appendix D, a number of approaches were considered and a MAIC approach was deemed to be most appropriate. Differences in the administration of placebo in the PDC comparator arms are acknowledged as a limitation of the MAIC analysis however, for the purpose of ITCs, placebo + PDC (AEGEAN control arm) and neoadjuvant chemotherapy (CheckMate 816) were treated as common comparators and assumed equivalent. Other factors in addition to control arm characteristics were considered in the feasibility assessment, including differences between trials in patient baseline characteristics. This included region of enrolment, with differences between trials in region (Asia vs non-Asia) accounted for as part of the MAIC. It is not possible to say categorically what the impact adding placebo to the control arm of the CheckMate 816 trial would have had on the treatment effect. CheckMate 816 was an open-label trial which did not include a placebo in the control arm to match the addition of nivolumab to PDC in the intervention arm. If the hypothesis made by the EAG that the addition of placebo to the control arm of the CheckMate 816 trial might improve efficacy in the CheckMate 816 control arm was true, this would reduce the relative treatment effect of neoadjuvant nivolumab + PDC vs the CheckMate 816 control arm. Accordingly, any bias in the ITC due to placebo would be in favour of nivolumab + PDC*".[5]
- The EAG thanks the company for the above response and agree that the comparator arm being different in the two comparisons would probably exert a conservative effect in favour of nivolumab. This is therefore not a concern.
- The covariates in the propensity score weighting should ideally have covered all the variables that were considered for the perioperative durvalumab versus perioperative placebo sub-group analyses (see Section 3.2.5.5), as all these were assumed to be effect modifiers. However, the variables of age, ECOG PS, race and lymph node station, which were included in the sub-group analyses, were not included in the MAIC propensity score weighting. The company were asked[4] to explain why these variables were not selected, and to perform another analysis with these variables included.
- The company responded by stating that, "*Race and lymph node station were not reported as baseline characteristics in CheckMate 816 and therefore, could not be included as covariates in the propensity score weighting used in the anchored MAIC. In contrast, age (<65 years versus ≥65 years) and ECOG status (0 versus 1) at baseline were available from both studies. Based on the criteria used in the ITC feasibility assessment to select potential effect modifiers (Appendix D.2.1) however, age and ECOG status were not considered to be potential treatment effect modifiers and were not selected as variables for weighting in the MAIC. In addition, Age and ECOG status at baseline were also generally well-balanced between AEGEAN and CheckMate-816 trials (see Appendix D.2.2.2). To explore the impact of including these variables in the MAIC, additional sensitivity analyses have been carried out in which both*

age (<65 years versus ≥65 years) and ECOG status (0 versus 1) at baseline have been included as factors in the weighting, in addition to those included in the base case and additional scenario. In both cases, the results of these sensitivity analyses were consistent with those presented in Document B.2.9, as shown in the results tables below."[5]

Table 3.25: MAIC sensitivity analysis EFS HRs for perioperative durvalumab versus neoadjuvant nivolumab + PDC (after weighting in the base-case and scenario 1 + inclusion of age and ECOG)

Comparison	Scenario	EFS HR	LCL (95%)	UCL (95%)
Perioperative durvalumab versus neoadjuvant nivolumab + PDC	Base-case	[redacted]	[redacted]	[redacted]
	Base-case + age and ECOG	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]
	Scenario 1 + age and ECOG	[redacted]	[redacted]	[redacted]

Based on Table 13, company response to clarification[5]

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.

Age and ECOG PS at baseline was included as additional factors in the weighting for the "… + age and ECOG" analyses.

CS = company submission; DSU = Decision Support Unit; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; HR = hazard ratio; LCL = lower confidence limit; 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

Table 3.26: MAIC piecewise EFS HRs (0-to-3-months and 3+ month time intervals) for perioperative durvalumab versus neoadjuvant nivolumab + PDC (after weighting in the base-case and scenario 1 + inclusion of age and ECOG)

		0–3 m 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	Base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Base-case + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Scenario 1 + age and ECOG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 14, company response to clarification[5]

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.

Age and ECOG PS at baseline was included as additional factors in the weighting for the "… + age and ECOG" analyses

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

Comparison	Scenario	0–3 m time interval			3+ m time interval		
		EFS HR	LCL (95%)	UCL (95%)	EFS HR	LCL (95%)	UCL (95%)
cell death ligand-1; PDC = platinum-doublet chemotherapy; PS = Performance Status; TSD = Technical Support Document; UCL = upper confidence limit							

Further information from these analyses (baseline characteristics post-weighting; ESS and distribution of weights) are provided below.

Table 3.27: Baseline characteristics in CheckMate 816 and AEGEAN (unweighted and after weighting to match CheckMate 816 in the base-case and scenario 1 + inclusion of age and ECOG)

Characteristic	CheckMate 816 (N=358)		AEGEAN unweighted (N=740)		AEGEAN Base-case + age and ECOG (ESS=[redacted])	AEGEAN Scenario 1 + age and ECOG (ESS=[redacted])
	n	%	n	%	%	%
Age: <65 years	176	49.2	358	48.4	[redacted]	[redacted]
ECOG PS: 0	241	67.3	506	68.4	[redacted]	[redacted]
Planned platinum chemotherapy: cisplatin	258	78.2	196	26.5	[redacted]	[redacted]
Histology: non-squamous	176	49.1	375	50.7	[redacted]	****
PD-L1 expression: <1%	155	46.5	247	33.4	[redacted]	[redacted]
PD-L1 expression: ≥50%	80	24.0	216	29.2	[redacted]	[redacted]
Region: Asia	177	49.4	305	41.2	[redacted]	[redacted]
Sex: Female	103	28.8	210	28.4	[redacted]	[redacted]
Smoking status: never	39	10.9	107	14.5	[redacted]	****
Stage: IIIA	-	57.4	338	45.7	[redacted]	[redacted]
Stage: IIIB	-	12.1	187	25.3	[redacted]	[redacted]

Based on Table 15, company response to clarification[5]

Characteristics with imbalance (≥5% difference) between CheckMate 816 and AEGEAN (red text).

Characteristics included in the weighting to match CheckMate 816 (blue fill).

For CheckMate 816, % PD-L1 expression is calculated using the PD-L1 evaluable population as the denominator (N=333; ~7% not evaluable for PD-L1 expression), and % stage is based on reclassification of patients according to AJCC 8th edition.

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.

Age and ECOG PS at baseline was included as additional factors in the weighting for each scenario.

DSU = Decision Support Unit; EFS = event-free survival; ESS = effective sample size; 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; TSD = Technical Support Document; UCL = upper confidence limit

Table 3.28: ESS of AEGEAN (weighted to match CheckMate 816) in the base-case and scenario 1

Arm	Scenario	N	Mean weight	Median weight	SD weight	Min weight	Max weight	ESS (%)
Perioperative durvalumab + neoadjuvant PDC	Base-case + age and ECOG	[redacted]						
Perioperative placebo + neoadjuvant PDC	Base-case + age and ECOG	[redacted]						
Perioperative durvalumab + neoadjuvant PDC	Scenario 1 + age and ECOG	[redacted]						
Perioperative placebo + neoadjuvant PDC	Scenario 1 + age and ECOG	[redacted]						

Based on Table 16, company response to clarification[5]

ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; PDC = platinum-doublet chemotherapy; SD = standard deviation

Figure 3.10: Distribution of rescaled weights of AEGEAN (weighted to match CheckMate 816) in the base-case and scenario 1

Based on Figure 2, company response to clarification letter[5].

EAG comment:

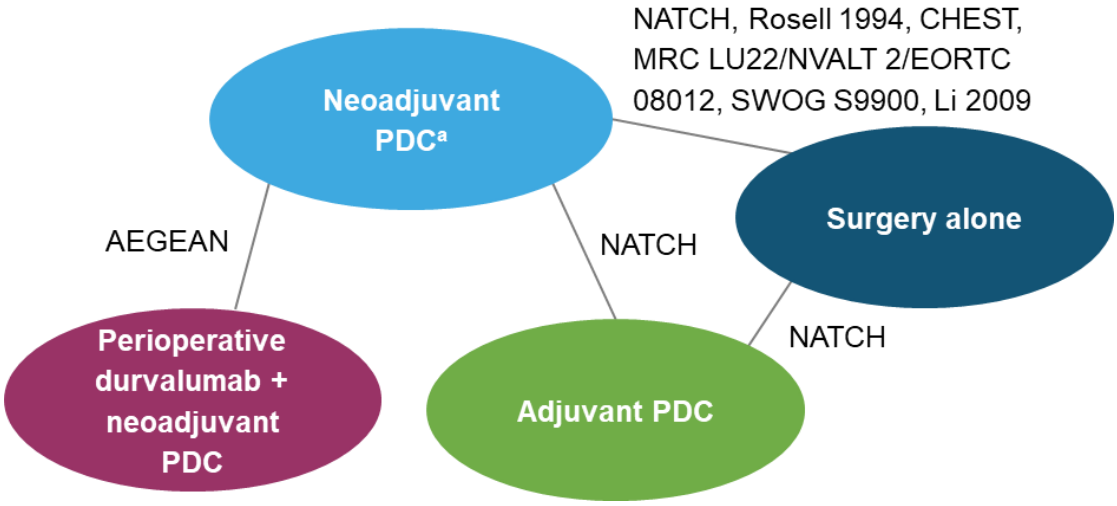
- The EAG thanks the company for the above response, comprising a sensitivity analysis including ECOG PS and age in the MAIC. The EAG agrees that the sensitivity analysis does not change the results qualitatively. The EAG also note that the inclusion of age and ECOG PS actually improves the estimates for the relative efficacy of perioperative durvalumab, reducing any concern that the previous omission of these variables from the MAIC would bias results in favour of the study drug.

- Only EFS was subjected to MAIC analysis, but the rationale for this is not explained. The company were asked to clarify this.[4]
- The company responded by stating that, "*Event-free survival was considered the most relevant outcome for the ITCs as it assesses the full perioperative approach as defined by the NICE final scope, considers the occurrence of multiple patient-relevant events, provides a direct measure of treatment efficacy across both neoadjuvant and adjuvant treatment periods with surgery as a curative intent therapeutic strategy, and is not confounded by subsequent therapy following progression or recurrence. Surgery with neoadjuvant and/or adjuvant therapy is given with curative intent, with the aim to completely remove the primary tumour and reduce the risk of any subsequent recurrence. Progression precluding surgery or recurrence after surgery are both highly relevant events for patients, given the impact of progression/recurrence on subsequent prognosis and HRQoL. In AEGEAN, EFS is defined as the time from randomisation to an event of disease progression that precludes surgery, local or distant recurrence, or death due to any cause. Since EFS includes progression events precluding surgery, recurrence events after surgery, and death, it is aligned with the treatment goals of this setting and measures the success/failure of neoadjuvant followed by adjuvant therapy. In addition to the intrinsic value of EFS as an endpoint in this setting, EFS is also a surrogate for OS. Overall survival is evaluated in AEGEAN; however, a longer trial follow-up is needed as at the time of EFS IA1, OS data had 22% maturity and per the MTP, OS was not formally assessed. Thus, for early-stage NSCLC therapies such as perioperative durvalumab, the outcome of EFS, which considers multiple patient-relevant events (disease progression precluding surgery, disease recurrence after surgery, and death) and is also a surrogate outcome for OS, has more value in this setting. The second primary outcome of AEGEAN was pCR but this was not considered an outcome of interest for ITC. Pathological complete response is an early indication of treatment efficacy and a stringent indication of response to treatment in the neoadjuvant setting. Due to the early nature of the resectable NSCLC and its improved prognosis versus metastatic disease, pCR is an endpoint that is highly relevant to patients with resectable NSCLC receiving neoadjuvant therapy. However, the potential impact of adjuvant therapy on long-term outcomes (EFS and OS) is not captured by pCR. As such, EFS is considered a more relevant outcome to evaluate the full perioperative approach of durvalumab by ITC to inform the cost-effectiveness model. Quantitative synthesis of safety data was not conducted as it was considered inappropriate given the differences in treatment regimens and the sparseness of the data across the studies. Adverse events of the different treatment regimens have been taken into account in the cost effectiveness model, informed by safety data from the AEGEAN trial (Grade 3-4 AEs with incidence ≥ 5% in any treatment arm) for AEGEAN therapies and literature (for non-AEGEAN therapies).*"[5]
- In response to the above statement, the EAG would argue that outcomes other than EFS have been designated by NICE as relevant to the proper evaluation of the intervention, and therefore these should have been analysed, as far as possible, in accompanying MAICs. One outcome cannot determine the superiority of one treatment over another, given that different outcomes respond differently, and therefore an appraisal of superiority utilising only one outcome is incomplete and invalid. This is a key issue.

3.4.2 NMA

The network diagram for the NMA is given below (Figure 3.11).

Figure 3.11: Distribution network diagram of mITT AEGEAN versus adjuvant PDC and surgery alone, base-case



Based on Figure 14, CS[3]
[a] In AEGEAN, placebo + PDC was the neoadjuvant PDC arm.
CS = company submission; mITT = modified intention-to treat; PDC = platinum-doublet chemotherapy

Four sensitivity analyses were carried out, that involved exclusion of some studies from the network to reduce inconsistency. Table 3.29 summarises these analyses.

Table 3.29: List of studies excluded from mITT population sensitivity analyses

Population	Analysis	Description	Reason for exclusion in sensitivity analysis
mITT	**Base-case**	**All studies**	**NA**
mITT	Sensitivity analysis 1	Excludes Rosell 1994, MRC LU/22/NVALT 2/EORTC 09012	Exclude studies with 2G chemotherapy
mITT	Sensitivity analysis 2	Excludes Rosell 1994, Li 2009	Exclude studies with stage III patients only
mITT	Sensitivity analysis 3	Excludes Li 2009	Exclude Asia only studies
mITT	Sensitivity analysis 4	Excludes Rosell 1994, MRC LU/22/NVALT 2/EORTC 09012, Li 2009	Exclude studies for any of the reasons above

Based on Table 22, CS[3]
2G = second generation; EORTC = European Organisation for Research and Treatment of Cancer quality of life; mITT = modified intent-to-treat; NA = not applicable

EAG comment:

- There is clinical heterogeneity across studies and between comparisons in terms of the treatments (i.e., 'neoadjuvant PDC' means different things in different papers) and populations. The sensitivity analyses put forward by the company appear insufficient to account for this. All the sensitivity analysis models have a better fit to the data than the base-case, as shown by their much lower Deviance Information Criteria (DIC) values (See CS, Appendix, Table 45) but it is unclear how consistency models and inconsistency models compare to each other for each scenario. The company were asked[4] to give an overview of clinical heterogeneity and to provide

the DIC values for the consistency and inconsistency models for the base-case and all the sensitivity analyses.

- The company responded by stating that, "*Appendix D describes the NMA in detail. Specifically, D.2.1 describes the feasibility assessment for NMA and D.2.3 describes the NMA methodology. Heterogeneity was considered throughout the feasibility assessment and analysis methodology. The DIC values are reported in Appendix D, Table 45. Consistency should be assessed when there are closed loops of direct evidence on three or more treatments that are informed by at least three independent sources of evidence. In the case of this ITC, the shape of the network does not allow for the fitting of inconsistency models due to the absence of a loop containing both 'direct' and 'indirect' evidence. The only loop contained in the network is the 'direct' evidence from the multi-arm NATCH trial. This applies to both the base case and sensitivity analyses*."[5]
- With respect to the company statement above, the EAG does not agree that the only loop in the NMA is formed solely by the multi-armed NATCH trial in the base-case. As Figure 3.11 shows, the neoadjuvant PDC versus surgery comparison in the loop is contributed to by four trials additional to NATCH. The estimate for this arm will therefore not automatically be consistent with the other two arms (as it would have been had that arm been solely dependent on the NATCH data). Therefore, the consistency of this loop could and should have been estimated, by comparing DIC values for the consistency and inconsistency models. This remains a key issue.
- The AEGEAN trial is connected to all relevant comparators, as evidenced by the conduct of anchored ITCs with all comparators. However, the ITCs were separated into one for versus only neoadjuvant nivolumab and an NMA for adjuvant PDC and surgery alone. The company were asked to clarify several points.[4] Firstly, they were asked why the estimation of perioperative durvalumab versus neoadjuvant nivolumab was not approached through an all-encompassing NMA (that would cover all three decision problem comparators). They were asked to conduct an NMA that includes all three comparators. For the NMA, given the clinical heterogeneity between trials, the company was asked to employ the method of multi-level network meta-regression as mentioned by the company in Appendix D and recommended by Phillippo et al. 2020.[24]
- The company responded by stating that, "*As described in Appendix D, a feasibility assessment resulted in a MAIC being chosen as the most appropriate approach for the comparison of perioperative durvalumab versus neoadjuvant nivolumab + PDC. Since individual patient data (IPD) were available for AEGEAN, both NMA and population-adjusted indirect comparison (PAIC) methods were considered as part of the ITC feasibility based on the methods recommended in NICE DSU TSDs. Multilevel network meta-regression (ML-NMR) is not currently recommended as part of NICE DSU TSD guidance and so was not ultimately explored. As described in Appendix D, a PAIC approach was considered to account for differences between baseline characteristics deemed effect modifiers in AEGEAN and CheckMate 816. No formal guidance exists for selecting between the MAIC and STC as PAIC approaches and evidence in literature review and simulation paper studies is mixed on which approach performs better. The theory behind the two approaches was carefully reviewed and a MAIC was considered the method that has less assumptions and is more flexible to perform endpoint analysis by using weighted data. In addition, MAIC approaches have been utilised in a large number of cases in HTA where PAIC have been considered, and so MAIC was also seen as the more established method. Given this rationale, it is not deemed necessary to run an STC*

for the perioperative durvalumab versus neoadjuvant nivolumab + PDC comparison. Heterogeneity between studies with adjuvant chemotherapy and surgery were identified however, as described in the submission, in the absence of a clear candidate for pairwise PAIC (and to include evidence from multiple studies), NMA was considered for these comparisons (as per TA876), with sensitivity analyses conducted to explore the impact of heterogeneity between studies. Furthermore, there was insufficient information reported on key baseline characteristics (that were considered potential effect modifiers) from the adjuvant chemotherapy and surgery studies to feasibly conduct PAICs for these comparisons. For example, PD-L1 expression and smoking status at baseline were not reported from these studies, and differences in the staging system versions used between trials makes comparisons of (and adjustments relating to) disease stage very challenging. PAICs were therefore not considered for these comparisons. For the same reason, ML-NMR including comparisons versus adjuvant chemotherapy and surgery (as well as neoadjuvant nivolumab + PDC) would also not be considered feasible. No additional analyses have therefore been conducted."[5]

- The EAG response to the above is as follows. The company invoke the lack of recommendation in the NICE TSDs in refusing to conduct a ML-NMR. However, there is no requirement in the NICE methods guide to only use methods that are recommended in a TSD.[2] Indeed, there is an imperative to use the best available evidence. In this particular case, a limitation of a MAIC is that it only allows estimation of a treatment effect in the population consistent with the comparator dataset.[25] This might therefore create an inconsistency with the treatment effects with each of the other comparators estimated using the NMA: ML-NMR *"...can produce population-adjusted treatment effects for any target population with given covariate values, not just [a single] study population."* (p. 4889)[24]

The NMA was conducted using Bayesian methods, with a Monte Carlo Markov Chain simulation, using R. Both fixed effects and random effects models were used, and the random effects model was preferred given the better fit to the data, as shown by a lower DIC. The base-case and four sensitivity analyses were meant to have been conducted for 1) the overall period, and 2) 0-3 months/>3 months, but a low number of events in the 0-3 month time interval meant the model did not converge, and so the analyses were only for 1) the overall period, and 2) >3 months.

Figures 3.12 to 3.16 summarises the NMA results in the base-case and the four sensitivity analyses.

Figure 3.12: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (base-case)

Based on Figure 15, CS[3]
Base-case = all studies included.
CrI = credible interval; CS = company submission; EFS = event-free survival; HR = hazard ratio; mITT = modified intention-to-treat; PDC = platinum-doublet chemotherapy

Figure 3.13: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 1)

Based on Figure 16, CS[3]
Sensitivity analysis 1 = excludes studies with 2G PDC.
2G = second generation; CrI = credible interval; CS = company submission; EFS = event-free survival; HR = hazard ratio; mITT = modified intent-to-treat; PDC = platinum-doublet chemotherapy

Figure 3.14: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 2)

Based on Figure 17, CS[3]
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 3.15: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 3)

Based on Figure 18, CS[3]
Sensitivity analysis 3 = excludes Li 2009 (Asia only studies).
CrI = credible interval; CS = company submission; EFS = event-free survival; HR = hazard ratio; mITT = modified intention-to-treat; PDC = platinum-doublet chemotherapy

Figure 3.16: EFS HRs for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC, and surgery alone – mITT (sensitivity analysis 4)

Based on Figure 19, CS[3]
Sensitivity analysis 4 = excludes studies with 2G PDC, studies with stage III only patients, and Asia-only studies.
2G = second generation; CrI = credible interval; CS = company submission; EFS = event-free survival; HR = hazard ratio; mITT = modified intention-to-treat; PDC = platinum-doublet chemotherapy

The CS[3] summarises the NMA results as follows: "[redacted] *and as a result of excluding Rosell 1994 and Li 2009, statistical heterogeneity (I2) was reduced from* [redacted] *in the base case analysis to* [redacted] *in sensitivity analysis 2. The EFS HRs from the random effects NMA sensitivity analysis 2 in the overall period were* [redacted] *for perioperative durvalumab versus adjuvant PDC, neoadjuvant PDC and surgery alone, respectively. The results of sensitivity analysis 2 were used as estimates of relative efficacy in the cost-effectiveness model*."

EAG comment:

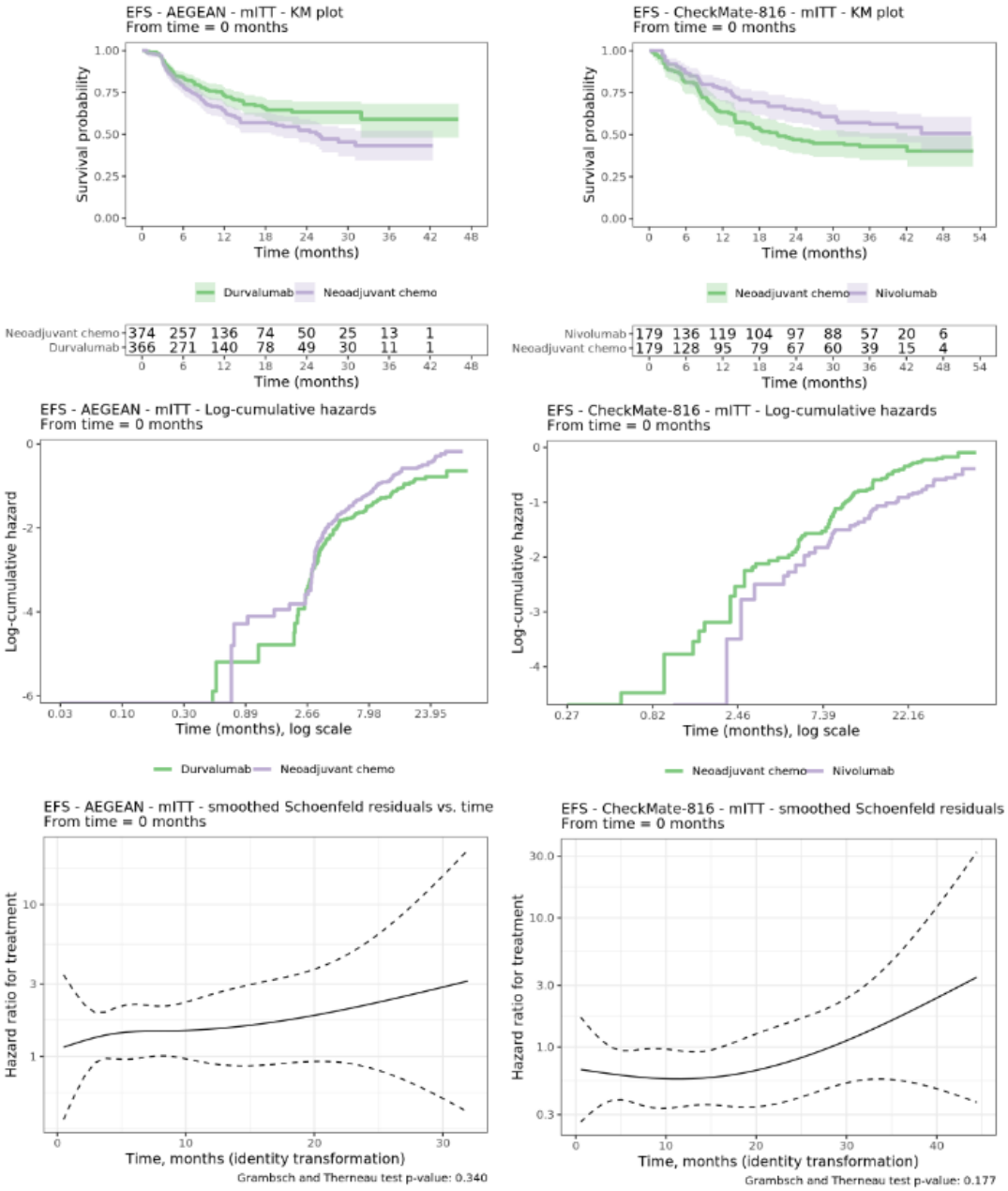
- The EAG would argue that outcomes other than EFS have been designated by NICE as relevant to the proper evaluation of the intervention, and therefore these should have been appraised, as far as possible, in accompanying NMAs. One outcome cannot determine the superiority of one treatment over another, given that different outcomes respond differently, and therefore an appraisal of superiority utilising only one outcome is incomplete and invalid. This is a key issue.
- The rationale for using the results from scenario 2 for the cost effectiveness model appears to be valid. The results for this scenario are not the most beneficial for the study intervention, which reduces any suggestion of a biased choice.
- The MAIC and the NMA both employed a Cox proportional hazards model, although a piecewise analysis, splitting the analysis into the 0-3 and >3 months epoch, was used to try to avoid the problem of the overall dataset not following the proportional hazards assumption

given the probable change in the HR between the 0-3 and >3 months periods observed in the AEGEAN trial. However, it appears that there was no consideration of non-proportional hazards after 3 months or between durvalumab and any of the comparators outside of the AEGEAN trial i.e. neoadjuvant nivolumab, surgery or adjuvant PDC. Therefore, a method of analysis that relaxes the proportional hazards assumption i.e. using time-dependent HRs would perhaps be more efficient. The company were asked[4] to conduct a NMA that employs a method allowing time-varying HRs such as that described by Cope et al. 2020, which was used in NICE TA865.[26, 27]

- The company responded by stating that, "*As described in the CS, the piecewise approach with 3 month cut-point was explored for perioperative durvalumab versus all comparators, based on delayed separation in the AEGEAN trial (perioperative durvalumab versus neoadjuvant PDC). Given the clear rationale for selecting the 3-month time point in AEGEAN (CS Section B.3.3.1) and the general applicability of this rationale to other neoadjuvant studies (e.g. in CheckMate-816 the first tumour assessment was also planned before surgery [within 14 days]), the piecewise method was deemed a parsimonious way to address the observed pattern and one that would reflect how EFS assessed in the clinical trials is assessed in clinical practice (see response to B.11). Figure 3.17 and 3.18 below show the observed EFS data, log-cumulative hazard plots and smoothed Schoenfeld residuals used to assess proportional hazards for both AEGEAN and CheckMate 816. The improvement in proportionality observed in AEGEAN when assessing only the 3+ months' time interval was not replicated in CheckMate-816. Similarly, evaluations of the proportional hazard assumptions for studies informing comparisons of surgery alone or adjuvant PDC versus neoadjuvant PDC yielded mixed results. In cases where there was separation between arms, a clear or consistent timepoint for this separation was not evident. Nevertheless, across all studies (excluding Rosell 1994 and Li 2012, as per the preferred NMA network*) [company references 13,15,39] *there is a consistent observation that there is minimal separation between curves during the first 3 months. Hence, a piecewise ITC was explored, utilising a 3+ months cut-point. This approach aligns with the clinical rationale and ensures consistency with the observed data in AEGEAN, and for nivolumab + PDC, the proportional hazards assumption is consistent with the company base case analysis in TA823.*[28] *In the cost-effectiveness model, hazard rations (HR)s derived from the piecewise ITC analyses were favoured. This preference was based on the fact that extrapolation was also performed in a piecewise manner. Additionally, this choice aligns with the expectation that none of the model treatments are anticipated to exhibit separation from neoadjuvant PDC within the first 3 months. A (cost-effectiveness) scenario analysis was conducted to assess the use of the piecewise approach in which the HRs from the ITC (overall period; assuming proportional hazards) was applied. The results were consistent with the 3-month plus piecewise results and demonstrated that model outcomes were minimally affected. This consistency is observed across all comparators. Regarding the request for a parametric NMA, the use of this approach (Cope 2020) requires use of survival distributions fitted to the observed data. However, fitting of survival distributions to the overall trial period in AEGEAN resulted in poorly fitting curves. This discrepancy led to the adoption of piecewise approach for extrapolation in the cost-effectiveness model. In conclusion, a piecewise approach is most appropriate. Further, reference to TA865 is not entirely relevant as it included advanced, unresectable patients being treated to progression with regular RECIST tumour assessments. A similar rationale for piecewise approach would not have been expected in this case*."[5]

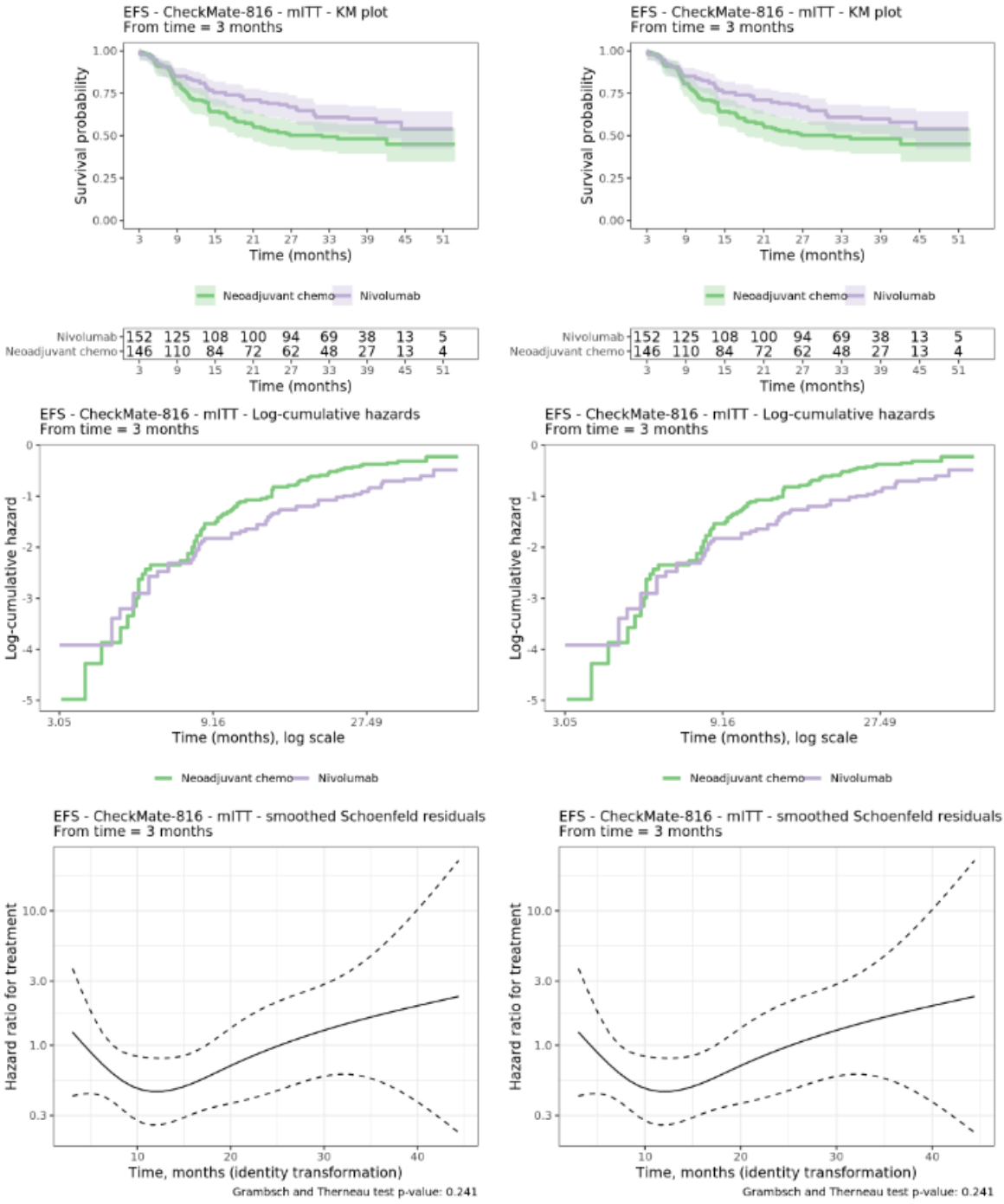
- It is unclear to the EAG why the company would not conduct the NMA allowing change in HRs over time, as could be implemented using the Cope et al. 2020 method.[26] It might be that the fit of survival distributions might not be ideal, but on the other hand assuming a fixed HR for most of the time horizon i.e. beyond 3 months might be more of a problem given that most of the plots of HR below seem to show considerable variation over time, including crossing the point of no difference (HR=1).[5] Therefore, this is a key issue.

Figure 3.17: Proportional hazards assessment for EFS in AEGEAN (mITT population) and CheckMate 816 from time = 0 months (i.e., full follow-up)



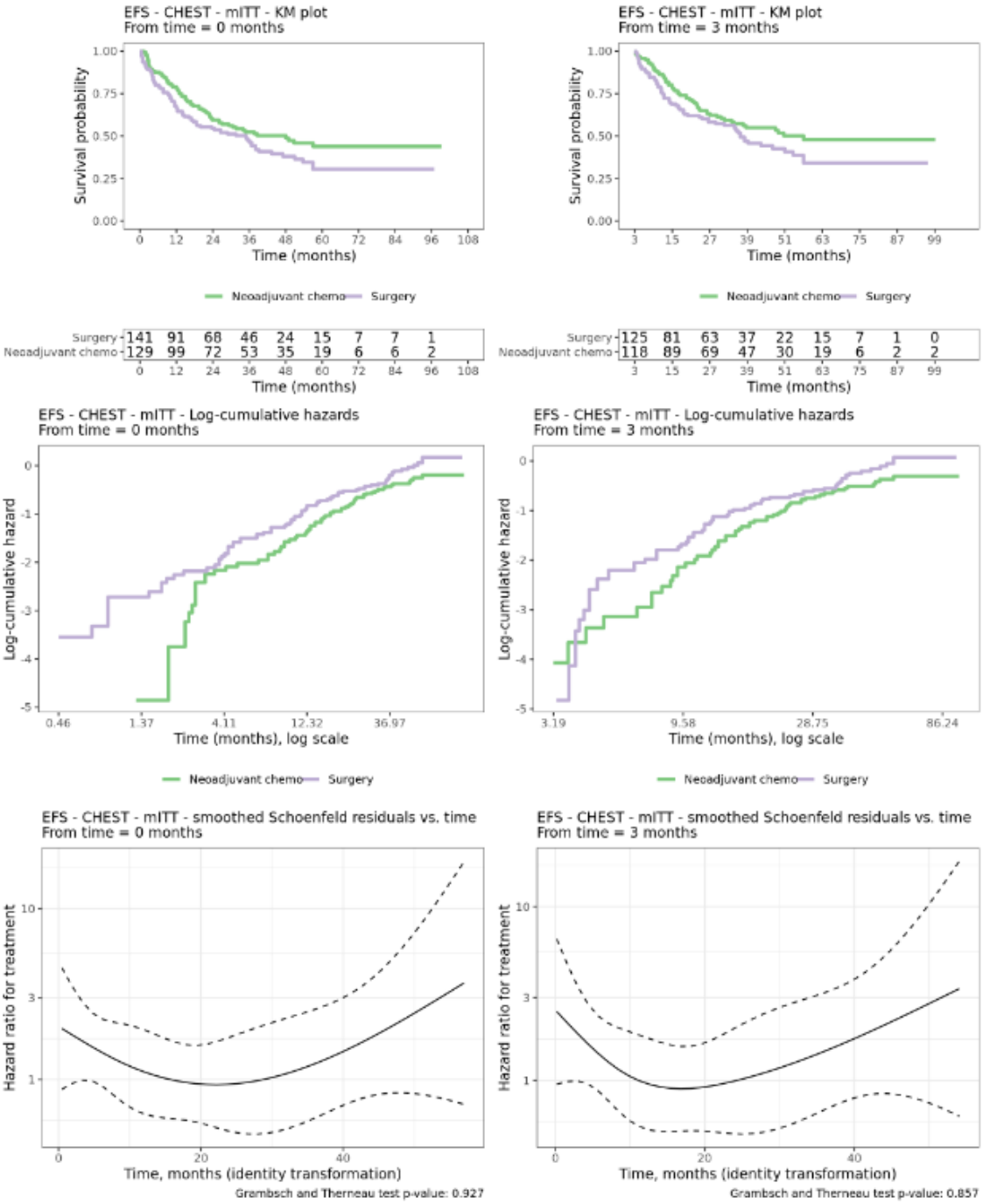
Based on Figure 3, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat

Figure 3.18: Proportional hazards assessment for EFS in AEGEAN (mITT population) and CheckMate 816 from time = 3 months (i.e., piecewise 3+ month interval)



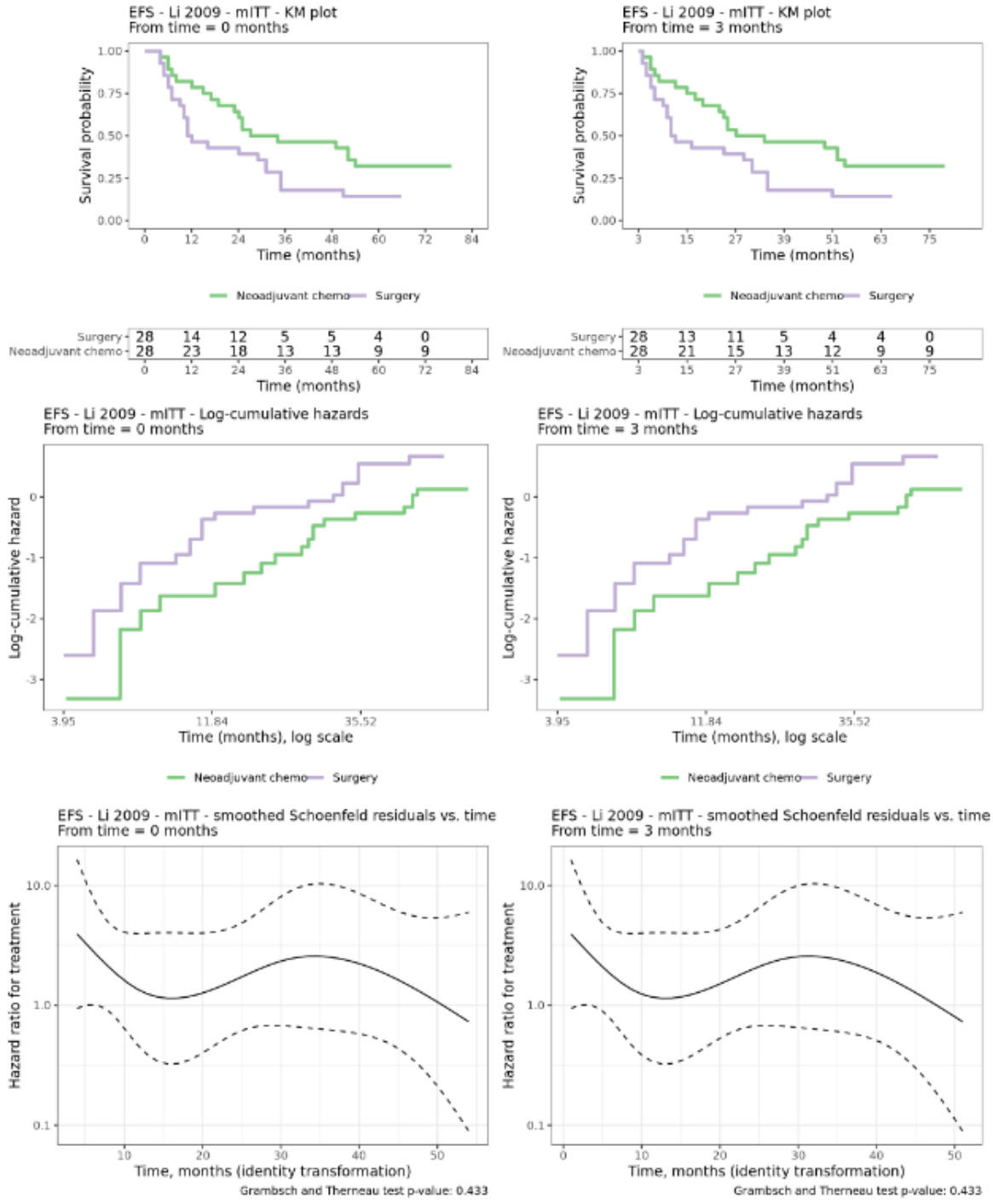
Based on Figure 4, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat

Figure 3.19: Proportional hazards assessment for EFS in CHEST (mITT population) from time = 0 months and from time = 3 months



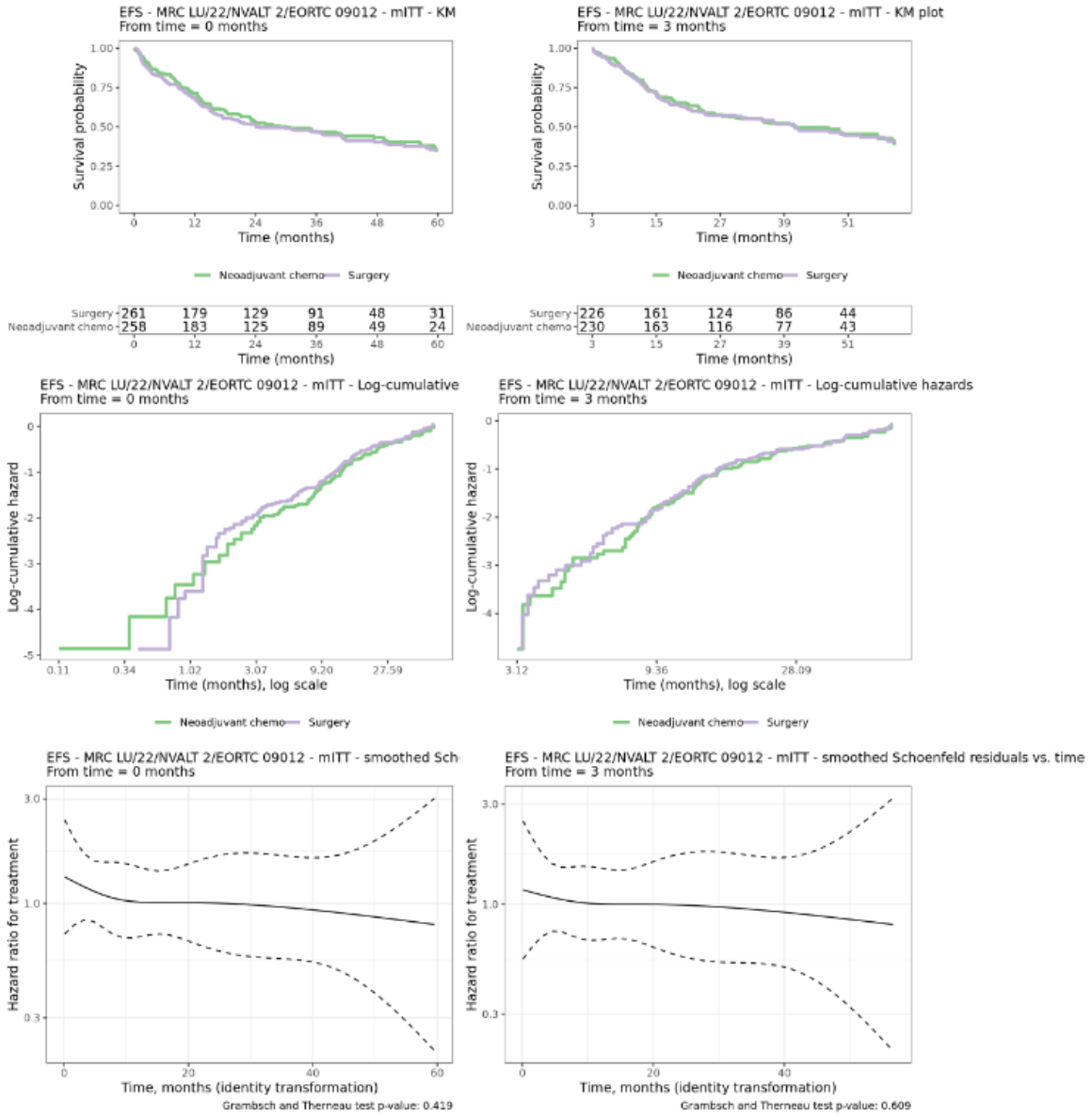
Based on Figure 5, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat

Figure 3.20: Proportional hazards assessment for EFS in Li et al. 2009 (mITT population) from time = 0 months and from time = 3 months



Based on Figure 6, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat

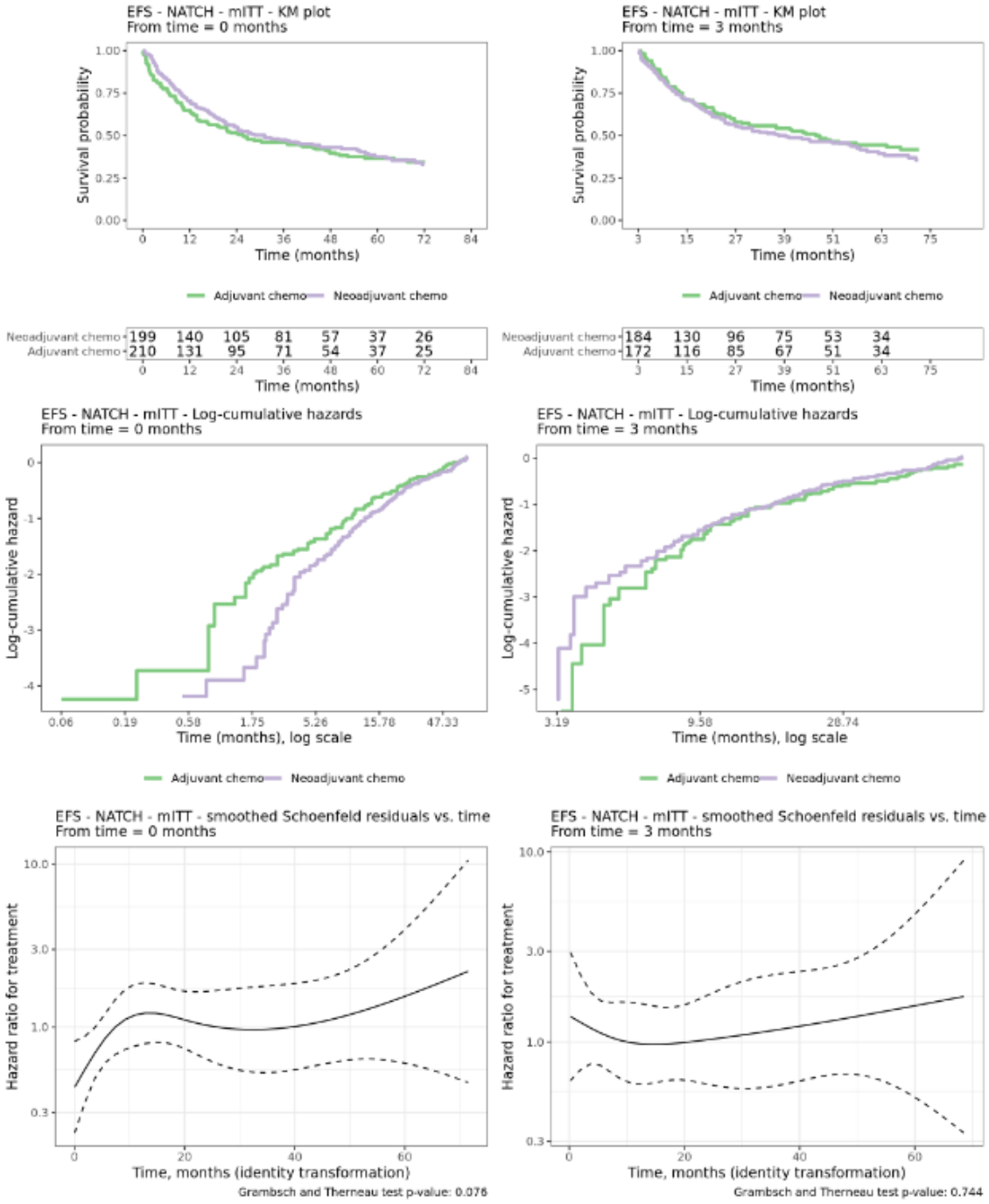
Figure 3.21: Proportional hazards assessment for EFS in MRC LU/22/NVALT 2/EORTC 09012 (mITT population) from time = 0 months and from time = 3 months



Based on Figure 7, company response to clarification[5]

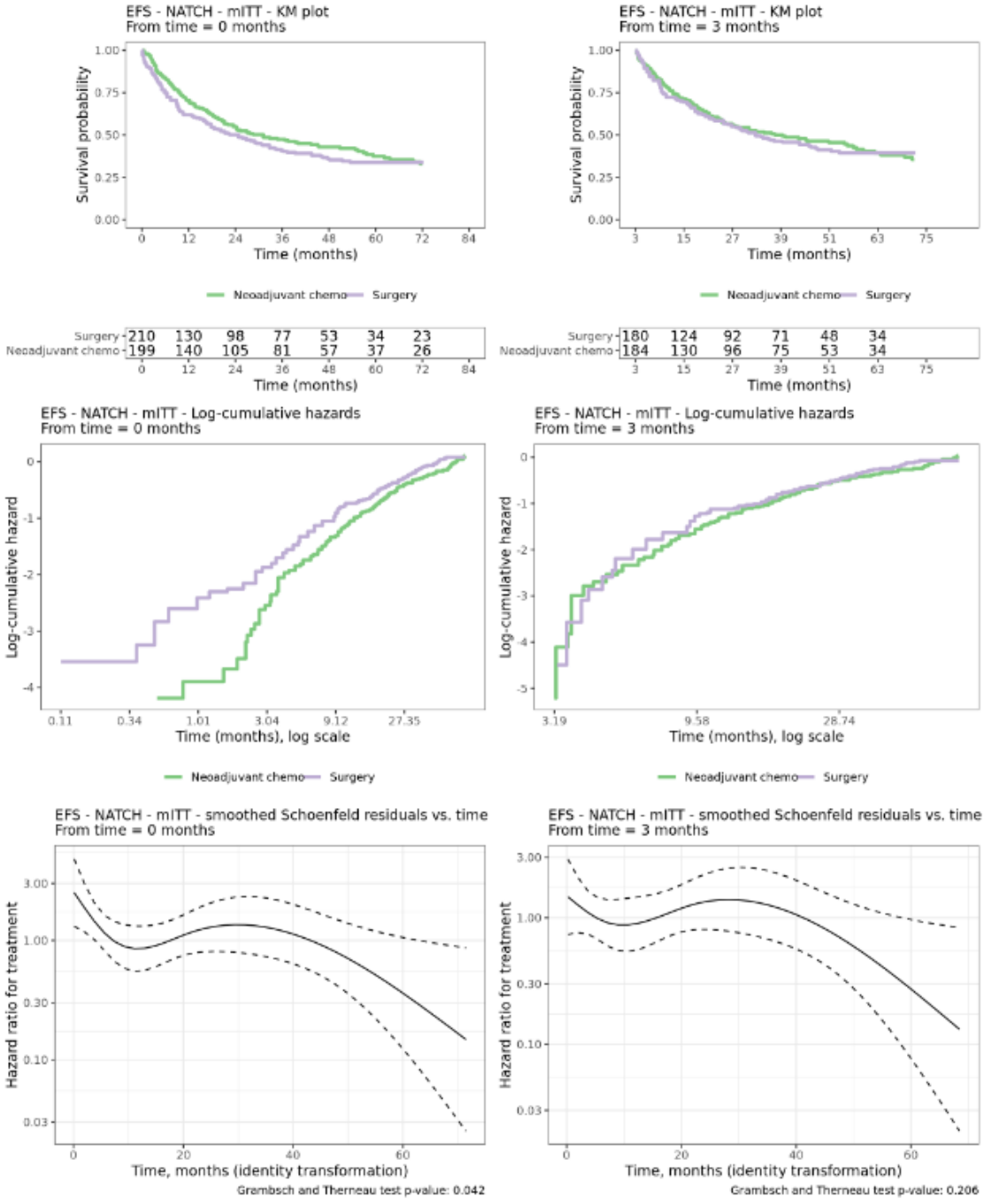
EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer quality of life; KM = Kaplan-Meier; mITT = modified intention-to-treat

Figure 3.22: Proportional hazards assessment for EFS in NATCH (adjuvant PDC) (mITT population) from time = 0 months and from time = 3 months



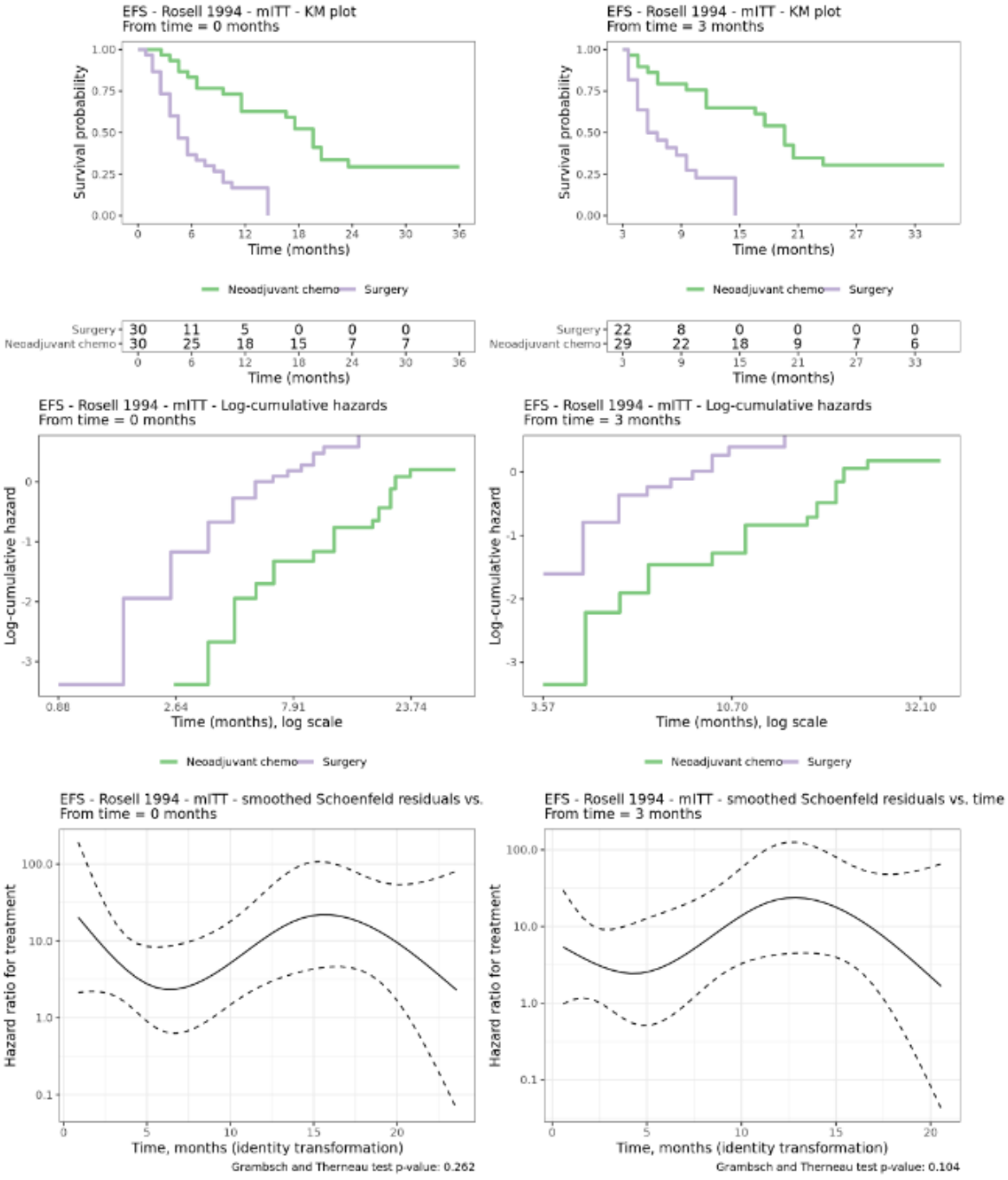
Based on Figure 3, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat; PDC = platinum-doublet chemotherapy

Figure 3.23: Proportional hazards assessment for EFS in NATCH (surgery) (mITT population) from time = 0 months and from time = 3 months



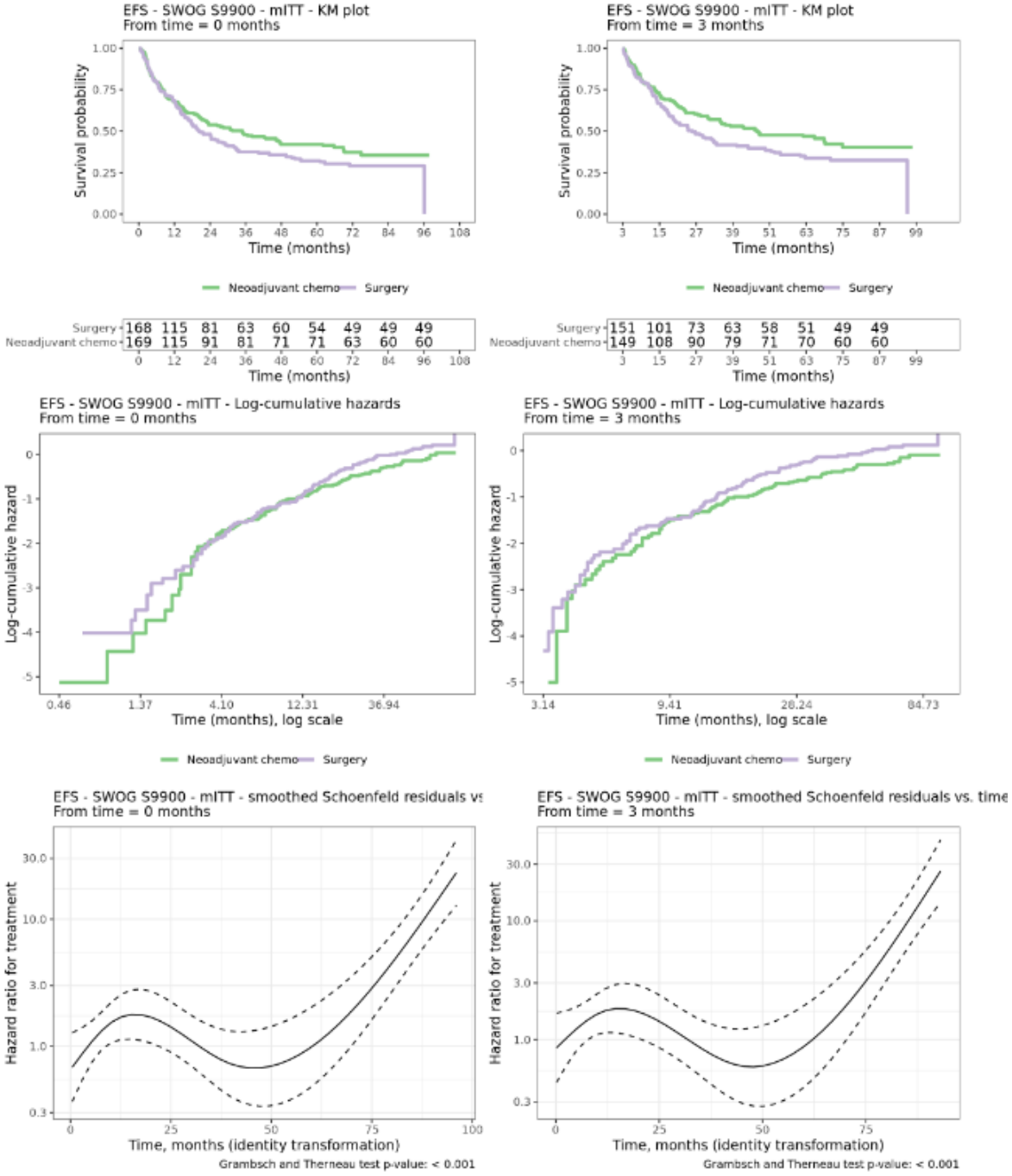
Based on Figure 9, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat

Figure 3.24: Proportional hazards assessment for EFS in Rosell et al. 1994 (mITT population) from time = 0 months and from time = 3 months



Based on Figure 10, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat

Figure 3.25: Proportional hazards assessment for EFS in SWOG S9900 (mITT population) from time = 0 months and from time = 3 months



Based on Figure 11, company response to clarification[5]
EFS = event-free survival; KM = Kaplan-Meier; mITT = modified intention-to-treat

3.5 Additional work on clinical effectiveness undertaken by the EAG

None.

3.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant the clinical efficacy and safety of perioperative durvalumab and relevant comparators.[3, 5, 10] Searches were conducted in July 2022 and updated in October 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted.

The NICE Final Scope[1] defined the population as people with untreated resectable NSCLC which has no EGFR or ALK genetic alterations. The NICE Final Scope[1] defined the intervention as neoadjuvant durvalumab with chemotherapy followed by adjuvant durvalumab monotherapy and the comparator as ECM. The company's decision problem differed from the NICE Final Scope[1] most significantly in terms of the omission of nCRT as a form of ECM. The EAG considers that nCRT cannot be legitimately excluded until objective evidence that nCRT is less effective than the other included comparators in this population has been provided, and such evidence has not been presented.

The included trial was a high quality double-blind RCT where the intervention was identical to that defined in the NICE Final Scope,[1] but the comparator was neoadjuvant placebo given alongside platinum-based chemotherapy with subsequent adjuvant placebo monotherapy. This demonstrated superior EFS for the intervention, with a HR of 0.68 (95% CI 0.53 to 0.88) at the primary analysis DCO. A benefit for the intervention was also observed for pCR, with a difference in proportions of 13.0% (95% CI 7.1 to 19.5) at the primary analysis DCO. There were also significant intervention benefits for MPR. However, results for DFS were not provided and the non-significant results for OS were not given formal status because of the dictate of the MTP. HRQoL [redacted] between intervention and comparator, which is an important factor for the committee to note. Part of the reason for these non-significant results or the inability to present outcome data is the immaturity of data. This leads the EAG to think that the company should have waited until the data were more mature before making a submission to NICE. In their current form, the data do not demonstrate efficacy against placebo across all NICE Final Scope[1] outcomes, and it cannot be assumed (until the data are presented) that more mature data will show efficacy.

The internal validity of these trial results appears to be high, but there are questions about the external validity. For the outcome of EFS, the sub-group analyses suggested there were possible outcome modifiers such as gender and smoking status. Likewise, for the outcome of pCR, the sub-group analyses suggested there were possible outcome modifiers such as for PD-L1 expression, lymph node station, disease stage, smoking status and geographic region. If these characteristics vary between the trial and UK target populations this might prevent the generalisability of findings from trial to UK target population. The company was unable to provide objective data describing the characteristics of the UK target population, relying instead on expert opinion. Hence, it was not possible to exclude differences in potentially effect-modifying characteristics and therefore was not possible to exclude possible threats to external validity.

The trial comparator was not a decision problem comparator, and so the company carried out i) an adjusted MAIC, and ii) an NMA to estimate the effects of the intervention against the decision problem comparators. These ITCs were subject to limitations. Firstly, the only outcome to be used in the MAIC or NMA was EFS, which meant that other outcomes of relevance such as HRQoL were not considered. One outcome cannot determine the superiority of one treatment over another, given that different

outcomes respond differently, and therefore an appraisal of superiority utilising only one outcome is incomplete and invalid. Other limitations were the failure to use one over-riding NMA rather than separate MAICs and an NMA, the lack of consistency testing in the NMA and the failure to use time-dependent HRs. These limitations add some uncertainty to the ITC findings that durvalumab has benefits over the comparators.

AEs were described as 'manageable' by the company, but the greater risk of 'deaths possibly related to any study treatment' in perioperative durvalumab compared to perioperative placebo has a relative risk of large magnitude, at 3.47 (95% CI: 0.73, 16.62). The 95% CIs suggest this result may be explained by sampling error, but because of the importance of the adverse outcome it would probably be prudent to consider the possibility that it represents a real population effect. The absolute risk difference of 0.01 (-0.00, 0.03) for this outcome implies, given a real population effect, that 1 in every 100 people with resectable NSCLC given perioperative durvalumab instead of perioperative placebo may die because of the treatment given, rather than because of the disease process or any other reason. The clinical significance of these adverse results, albeit uncertain, should therefore be weighed up against the benefits by the committee. It should be noted that the AEGEAN statistical analysis plan did not include formal statistical testing for AE results.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

Three SLRs were performed in patients with stage I-III NSCLC who are candidates for, or have previously undergone, surgical resection of the primary NSCLC with the objectives to identify and select relevant 1) cost effectiveness analysis studies (CS, Appendix G); 2) HRQoL or health state utility value (HSUV) studies (CS, Appendix H); 3) costs and healthcare resource use studies (CS, Appendix I).

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and resource use identification presented in the CS.[3, 10] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[11, 12] The EAG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS provided details of an SLR conducted to identify published economic evaluations in patients with stage I–III NSCLC who are candidates for, or have previously undergone, surgical resection of the primary NSCLC.[10] Searches were undertaken on 26 October 2023, 11 September 2023 and 14 November 2023.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations (as reported in CS)

Resource	Host/Source	Date Ranges	Date last searched
Electronic databases			
Embase	Ovid	1980-2023/11/14	14.11.23
MEDLINE (including MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of print)	Ovid	1946-2023/11/14	14.11.23
Additional resources			
NHS EED	CRD website	Up to 2015/04/Iss 2	26.10.22
International HTA Database	Internet	Not stated	14.11.23
Cost-Effectiveness Analysis Registry	Internet	Not stated	27.11.23
ScHARRHUD	Internet	Not stated	27.11.23
EQ-5D Publications Database	Internet	Not stated	27.11.23
HTA websites			
AWMSG CADTH Republic of Ireland: NCPE NICE PBAC SMC France: HAS Germany: IQWiG	Internet	Last 10 years	27.11.23

Resource	Host/Source	Date Ranges	Date last searched
Italy: AGENAS Spain: AEMPS			

AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AGENAS = Agenzia Nazionale per i Servizi Sanitari Regionali; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technology in Health; CRD = Centre for Reviews and Dissemination; CS = company submission; E5-5D = EuropQol 5-Dimension; HAS = Haute Autorité de Santé; NHS EED = National Health Service Economic Evaluation Database; HTA = Health Technology Assessment; IQWiG = Institute for Quality and Efficiency in Health Care; NCPE = National Centre for Pharmacoeconomics; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; ScHARRHUD = University of Sheffield Health Utilities Database; SMC = Scottish Medicines Consortium

EAG comment:

- The company reported that due to a high overlap in search results a single set of searches to identify relevant studies on cost effectiveness, HRQoL and cost/health care resource use were used to inform the SLRs reported in Appendix G, H, and I. Original searches were undertaken in October 2023 and updated on 11 September 2023 and 14 November 2023. The CS, Appendix G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[3, 5, 10]
- In addition to bibliographic database searches, a good range of Health Technology Assessment (HTA) organisation websites, and grey literature resources were searched. The bibliographies of all relevant SLRs and NMAs identified during the literature review were also handsearched, to identify any additional relevant studies for inclusion. Searches were well structured, transparent and reproducible.
- Database searches were limited to cost effectiveness references and cost/resource use studies published since 2012. No date limit was applied to the HRQoL searches. Conference proceedings in Embase were limited from 2020-2023. Searches were not limited by language of publication.
- None of the study design filters used were referenced, however all contained an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.
- The EAG noted that the search strategies in Appendix G contained the same limitations in regard to the missing terms "Stage 1 or Stage I" from the disease stage facet as reported in Section 3.1.1. At clarification the company responded "*Searches for evidence on costs and healthcare resource use were not rerun, with the review of clinical evidence prioritised for this response. The healthcare resource use-related inputs used in the model (e.g. for disease management costs) were based on those which have been used in recent NICE appraisals for therapies in resectable NSCLC".*
- After clarification the EAG noted that conference searching was also reported for Appendix G,[10] but no names or strategies were provided. However, results were reported in the PRISMA search flows for Appendix G, H & I. For this reason, they are not included in the Table above.

4.1.1.1 Searches for model input

EAG comment: The CS and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data on patients with stage I–III NSCLC who are candidates for, or have previously undergone, surgical resection of the

primary NSCLC.[3, 5, 10] Searches were conducted in October 2023 and updated on 11 September 2023 and 14 November 2023. Searches were transparent and reproducible, and comprehensive strategies were used. A broad range of databases, HTA organisation websites and grey literature resources were searched. Overall, the EAG has no major concerns about the literature searches conducted for the costs SLR.

4.1.2 Inclusion/exclusion criteria

In- and exclusion- criteria for the review on cost effectiveness studies, HRQoL studies and costs and resource use studies are presented in Table 4.2.

Table 4.2: Eligibility criteria for the SLRs

	Inclusion criteria	Exclusion criteria
Patient population	Adult patients (≥18 years old) with Stage I–III NSCLC who are candidates for surgical resection of the primary NSCLC (i.e. Stage I–III resectable NSCLC).	• Patients without NSCLC. • Patients with Stage IV NSCLC or metastatic NSCLC. • Patients with Stage I–III NSCLC who are not candidates for surgical resection of the primary NSCLC (i.e. Stage I–III unresectable NSCLC). • Children or adolescents (<18 years old).
Intervention/comparator	Any or no treatment for Stage I–III NSCLC prior to surgical resection of the primary NSCLC.	No planned surgical resection of primary NSCLC.
Outcomes(s) 1 (Published economic evaluations)	Economic evaluations reporting: • ICERs/ICURs • Cost per clinical outcome • Cost per utility • Total QALYs • Total LYGs • Costs (unit and total) • Incremental costs and QALYs	• Studies not reporting relevant outcomes. • Studies reporting relevant outcomes, but in a mixed population (e.g. patients with Stage I–III resectable and unresectable NSCLC) where outcomes are not reported separately for the Stage I–III resectable NSCLC population.
Outcomes(s) 2 (HRQoL studies)	Novel health state utility or disutility values or HRQoL values,* measured using any validated, published general or disease-specific instruments, including those measured by: • EQ-5D (3L or 5L) • SF-6D • HUI2/HUI3 • Time trade-off • Standard gamble • FACT-L • BPI-SF • LCSS • EORTC QLQ-C30 • EORTC LC-13	• Studies not reporting relevant outcomes. • Studies reporting relevant outcomes, but in a mixed population (e.g. patients with Stage I–III resectable and unresectable NSCLC) where outcomes are not reported separately for the Stage I–III resectable NSCLC population.

	Inclusion criteria	Exclusion criteria
	• FACIT	
Outcomes(s) 3 (Cost/resource use studies)	Novel direct or indirect cost or resource use data, relevant to a model of durvalumab in resectable stage I–III NSCLC. Including, but not limited to, cost and resource related to: • Disease monitoring • Hospitalisation • Surgery cost • Resource and costs associated with surgical complications • Treatment (drug and administration) • RT use • RT cost • Adverse effects • Out-of-pocket patient costs • Absenteeism and presenteeism	• Studies not reporting relevant outcomes. • Studies reporting relevant outcomes, but in a mixed population (e.g. patients with Stage I–III resectable and unresectable NSCLC) where outcomes are not reported separately for the Stage I–III resectable NSCLC population.
Study design 1 (Cost effectiveness analysis studies)	Economic evaluations of the following study designs: • Cost utility • Cost effectiveness • Cost consequence • Cost benefit • Cost minimisation • Budget impact	Any other types of analysis.
Study design 2 (HRQoL studies)	Any study design reporting novel health state utility/HRQoL data.	NA
Study design 3 (Cost/resource use studies)	Any study design reporting novel health state utility/HRQoL data.	NA
Publication type	• Journal records presenting original research • Conference abstracts published from 2020 onwards • HTAs	• Case studies/reports • Non-primary research studies, such as narrative review • Conference abstracts published prior to 2020
Other considerations	• Human subjects • Records with at least the abstract in the English language • Economic evaluations published in the last 10 years (2012 onwards)	• Animal studies • Records not in the English language • Analyses published pre-2012

Based on CS, Appendices[10] G, H, I

BPI-SF = Brief Pain Inventory Short Form; CS = company submission; EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = EuroQol Five Dimensions; FACIT = Functional Assessment of Chronic Illness Therapy; FACT-L = Functional Assessment of Cancer Therapy-Lung; HRQoL = health-related quality of life; HTA = Health Technology Assessment; HUI2/HUI3 = Health Utility Index 2/3; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-

	Inclusion criteria	Exclusion criteria
utility ratio; LCSS = Lung Cancer Symptom Scale; LYG = life-year gain; NA = not applicable; NSCLC = non-small-cell lung cancer; QALY = quality-adjusted life year; RT = radiotherapy; SF-6D = Short-Form Six Dimensions; SLR = systematic literature review		

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. CQ B1 requested justification for the exclusion of stage IV NSCLC was not included in the SLR. The company responded to suggest that the SLR was aligned with the population considered in the CS and the expected marketing authorisation for perioperative durvalumab. The EAG accepts the company's justification and thus, the rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion- criteria.

4.1.3 Results of reviews performed for cost effectiveness section

Appendices Tables 54 (Appendix G), Table 56 (Appendix G), 65 (Appendix I), and 75 (Appendix J) provide overviews of extracted results from the included economic evaluation studies, previous NICE HTA submissions, HRQoL studies, and cost and healthcare resource use studies, respectively. Potential applicability of included studies were considered in Table 64 (Appendix I) for HRQoL studies, and Table 74 (Appendix J) for cost and healthcare resource use studies.

EAG comment: The utilisation of the results extracted from the SLRs performed for the cost effectiveness section remains unclear to the EAG. For literature identified for data extraction, no overview was provided in CS, Section B.3.1 or in CS Appendices G, I, or H, regarding which extracted results were utilised to inform the economic model, nor justification provided for identified studies not utilised. While the company summarised the potential applicability of the HRQoL and cost and healthcare resource use studies included, it was unclear why exclusions were made. For example, a UK-specific study identified in the cost and healthcare resource use SLR was described as *largely applicable* in Table 74 of CS Appendix J, however, was seemingly not utilised to inform costs within the economic model.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with reference case
Perspective on costs	NHS and PSS	Consistent with reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with reference case

Element of HTA	Reference case	EAG comment on CS
Synthesis of evidence on health effects	Based on systematic review	Consistent with reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Consistent with reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Consistent with reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Unclear whether the UK tariff is used for all health state utilities
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with reference case

CS = company submission; EAG = External Assessment Group; EQ-5D = EuroQol five dimensions; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

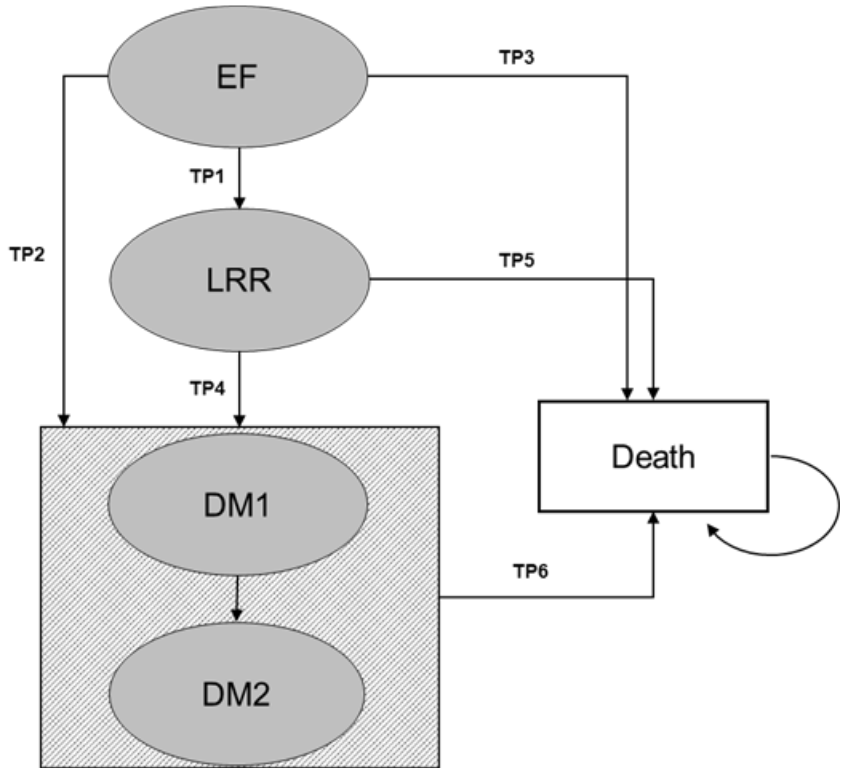
The company developed a de novo state-transition model in Microsoft Excel®, comprising of mutually exclusive health states that represent the disease course and survival for a cohort of patients that present with resectable early stage IIA/IIIB NSCLC (Figure 4.1). According to CS Figure 34, the economic model consisted of the following health states:

- event-free (EF),
- locoregional recurrence (LRR),
- distant metastases without further progression (DM1),
- distant metastases with further progression (DM2) and,
- death

Patients enter the model in the EF health state. From the EF state, patients can progress to either LRR (TP1), to DM (TP2), or to death (TP3). Patients transition to LRR from EF if they experience a LRR and can either receive active treatment or no treatment (i.e., best supportive care (BSC)). Patients receiving active treatment in LRR who then develop metastases or die transition to the DM (TP4) or death (TP5) state, respectively. For patients that received no treatment (BSC) in the LRR health state, the company assumed these could not transit to the DM health state but only to the death health

state (i.e., TP4 = 0% for the proportion of patients receiving BSC in the LRR health state). Patients who develop metastases and move to the DM state from either EF (TP2) or LRR (TP4), can only move to the death state (TP6) from this point onwards. For clinical plausibility the TP3, TP5 and TP6 (i.e. transitions to the death health state), were constrained to be the same as UK general population mortality, at a minimum.

Figure 4.1: Model structure



Based on Based on Figure 34 of the CS[3]
CS = company submission; EF = event-free; DM = distant metastasis; LRR = locoregional recurrence; TP = transition probability

EAG comment: The main concerns of the EAG relate to: a) the cure assumption; b) assumption that patients receiving BSC in the LRR health state cannot transit to the DM health state; c) the state transition modelling approach and; d) the use of EFS, and not DFS.

a) The CS stated that "*the model assumes that 95% of patients would achieve cure if they have not experienced an EFS event at 5 years*". In the CS this assumption was stated to be consistent with TA569 (early-stage breast cancer) and TA642 (relapsed or refractory acute myeloid leukaemia). Moreover, the cure assumption might be debatable as in the TA876 Final Appraisal Document (FAD) it was stated that "*The EAG considered that there was no convincing clinical evidence to support how the cure assumption had been modelled. It was noted that there is generally a consensus among clinical experts that cure occurs between years 5 and 8. But there is no consensus on the rates of cure, and the empirical evidence to support this assumption is lacking*". Moreover, it is unclear whether the cure assumption from TA569 and TA642 is appropriate given these appraisals consider different disease areas. In response to CQ B7 the company stated that the company's cure assumption was endorsed during the UK Advisory Board in January 2024. However, despite requested (CQ B26), the company did not provide further details related to this Advisory Board meeting (only a concise summary, that was not

reviewed by the clinical advisors, was available to the EAG). Moreover, according to the company's response to CQ B7, the total proportion of patients assumed to be cured (i.e. 95% of patients remaining in the EF health state at 5 years) was [redacted] for patients that received perioperative durvalumab, neoadjuvant PDC, neoadjuvant nivolumab + PDC, adjuvant PDC and surgery alone respectively. Based on the information available to the EAG, it was unclear whether these proportions as well as the assumption that cure involves maintaining an event-free status for patients until death is plausible. Given the uncertainty regarding the plausibility of the (implementation of the) cure assumption and lacking supporting empirical evidence, the EAG considers both the company's cure assumption as well as no cure assumption as potentially plausible scenarios. Consequently, the EAG base-case constitutes of a range reflecting this uncertainty. In addition, it would be informative if the company would conduct the scenario analyses requested in CQ B7, to explore the impact of this uncertainty.

b) The CS stated that an "*assumption was made that those patients who received BSC in LRR*" … "*would transition to the death state directly (i.e., not transition to DM and receive further treatment)*". In other words, patients receiving BSC in the LRR health state cannot transit to the DM health state. It is unclear to the EAG that this assumption would be clinically plausible and why this simplifying assumption was required. As patients receiving durvalumab are less likely to develop LRR (given the EFS HR), the proportion of patients affected by this simplifying assumption is lower for durvalumab than for the comparators. Moreover, the clinical expert opinion obtained by the EAG stated that "*it is too strong to say that patients receiving BSC could not transit to DM health state and only to death health state. Some patients may transit to the death health state after locoregional recurrence but many would develop metastatic disease and eventually succumb to their disease due to this*". Unfortunately, the company did not perform the scenario analyses requested in CQ B4, to explore the impact of this simplifying assumption.

c) The company adopted a state transition modelling approach, rather than the partitioned survival model that is also commonly used in oncology. State transition modelling allows using external sources of evidence and thus is not reliant on extrapolation of immature OS data. As stated in the CS, the use of state transition models may be deemed appropriate in cases where the cost effectiveness analysis requires a complex disease pathway to be analysed. In response to CQ B6, the company justified that "*Non-small cell lung cancer encompasses a diverse group of lung cancers, each with distinct histological and molecular characteristics. This heterogeneity leads to variations in disease progression, treatment responses, and overall outcomes. A state transition model allows for the incorporation of these diverse pathways, providing a more accurate representation of the disease. Additionally, treatment typically involves various lines of therapy, including surgery, chemotherapy, immunotherapies, and combinations. State transition models can capture the nature of these treatments and the transitions between different health states based on patient responses and disease progression. Finally, modelling resectable NSCLC requires long-term follow-up due to the potential for late-stage recurrences. State transition models allow for the simulation of extended time horizons, enabling the assessment of the long-term cost-effectiveness of different treatment plans.*"
Although a state transition approach might be reasonable, the implementation is potentially sub-optimal. Particularly given that time-dependent transition probabilities (TP4-6 in CS Figure 20) are estimated for the LRR and DM health states, i.e. to estimate the long-term costs and consequences. These parametric survival models are estimated based on external sources

of evidence, with transition probabilities as a function of the model cycle time (i.e. time dependent treatment probabilities). However, patients enter the LRR and DM health states at different points in time. Hence, the transition probabilities should be implemented as a function of the time since entry into the LRR or DM health state rather than as a function of the model cycle time. This erroneous implementation of time dependent transition probabilities might bias the estimated cost and consequences. In CQ B6 the company is asked to elaborate on the implications of the erroneous implementation of time dependent transition probabilities and report on the potential impact on the estimated costs and consequences using scenario analysis. Unfortunately, this was not addressed by the company. As a result, it is unclear to what degree the time-dependent transition probabilities for TP4-6 do bias the estimated outcomes.

d) According to the CS, EFS is defined as *"time from randomisation to an event of disease progression that precludes surgery, local or distant recurrence, or death due to any cause*" and DFS is defined as "*time from resection until local or distant disease recurrence in the subpopulation of patients who were disease-free following resection, or death due to any cause, whichever occurs first*". The company justified the EFS, and not DFS, to inform the current model in clarification response B12 by stating that "*DFS is analysed in the modified resected set (i.e., only includes patients with R0/R1 resection margins, and no evaluable disease on the first scan following surgery), with the time to recurrence or death events measured from the date of surgery. DFS therefore assesses the effect of adjuvant therapy following surgery, and in doing so only evaluates efficacy in a subset of patients included in AEGEAN (i.e., those receiving adjuvant therapy after surgery), and does not include events (e.g., progression or death) leading up to surgery. DFS results should therefore be considered in conjunction with other outcomes (e.g., the proportion of patients receiving surgery and achieving R0/R1)*". The EAG believes this is reasonable.

4.2.3 Population

Consistent with the anticipated indication for perioperative durvalumab, the population considered in the CS was adults with resectable NSCLC stages IIA to IIIB (N2 only), according to the American Joint Committee on Cancer (AJCC) staging 8th edition, whose tumours have no EGFR mutations or ALK aberrations (i.e., the mITT population included in the primary analysis of the AEGEAN trial). The population according to the Final Scope issued by NICE is people with untreated resectable NSCLC which has no EGFR or ALK genetic alteration.

The key baseline patient and disease characteristics that were used in the economic model are reported in Table 4.4.

Table 4.4: Key baseline patient and disease characteristics used in the economic model

Characteristic	Mean	SE
Age (years)	64.0	0.32
Male (%)	71.6	0.07
Average weight (kg)	[redacted]	[redacted]
Average height (cm)	[redacted]	[redacted]
BSA (m2)	[redacted]	[redacted]
PD-L1 ≥1%	66.6	NA
PD-L1 ≥50%	29.2	NA
Non-squamous histology (%)	50.7	NA

Characteristic	Mean	SE
Squamous histology (%)	49.3	NA
Based on company's economic model BSA = body surface area; cm = centimetres; kg = kilograms; m^2 = square metres; SE = standard error		

EAG comment: The main concerns of the EAG relate to a) not considering subgroups in the cost effectiveness analyses conducted by the company, and b) the generalisability of the AEGEAN trial population to the target population in UK clinical practice.

a) The NICE Final Scope states that subgroups should be considered (if the evidence allows) based on 1) whether durvalumab is used before and after surgery, 2) PD-L1 tumour proportion score and 3) disease stage. The company stated that "*Whilst pre-specified subgroup data from AEGEAN are presented in this submission, including for PD-L1 expression and disease stage (Section B.2.7), the cost-effectiveness analysis is based on the full mITT*". The EAG noted that clinical advisors in the summary report of the Advisory Board provided by the company stated that disease stage and PD-L1 expression were expected to be amongst the stronger potential EFS effect modifiers. In response to the clarification letter, the company argued that given the perioperative nature of the treatment being appraised, conducting subgroup analyses based on treatments before or after is not appropriate or relevant in a cost effectiveness analysis. Regarding the subgroup analysis for PD-L1 expression, the company noted that there was a consistent treatment effect across the mITT population and PD-L1 subgroup. Moreover, the company argued that the expected regulatory license will not include a restriction based on PD-L1 status and therefore maintained focus on the overall mITT population. Although the EAG appreciates the pre-specified subgroup data from the AEGEAN trial that are presented in the clinical effectiveness section of this submission, it would additionally like to see cost effectiveness analyses conducted based on these subgroups.
b) It is unclear whether the AEGEAN trial population is representative of the target population in UK clinical practice due to the lack of objective data provided on the characteristics of the UK target population. Subgroup analyses in the clinical effectiveness section of the CS suggested there may be important effect modifiers, and differences between the trial and UK target population may therefore influence the generalisability of trial findings to the UK target population. Further details regarding this key issue are discussed in Section 3.2.5.7 of this report.

4.2.4 Interventions and comparators

The intervention considered in the CS was durvalumab, administered intravenously (IV) at a dose of 1,500 mg in combination with PDC every 3 weeks (Q3W) for a maximum of four cycles (neoadjuvant period) followed by 1,500 mg IV every 4 weeks (Q4W) for a maximum of 12 cycles (adjuvant period).

The comparators considered in the CS were neoadjuvant PDC, neoadjuvant nivolumab with PDC, surgery alone (assumed to represent active monitoring) and adjuvant PDC. The NICE scope additionally listed nCRT, pembrolizumab and atezolizumab after adjuvant cisplatin-based chemotherapy as comparators. The company justified that these were not considered relevant comparators by stating that pembrolizumab is subject to an ongoing NICE appraisal, atezolizumab monotherapy is only recommended for use in the Cancer Drugs Fund (CDF), and nCRT is not offered to patients with resectable NSCLC in UK clinical practice according to UK clinical experts.

EAG comment: The main concern of the EAG relates to the exclusion of nCRT as a comparator. Although it was mentioned as a relevant comparator in the NICE Final Scope and is recommended in NG122, the company excluded nCRT as a comparator in the economic model. The EAG's clinical expert agrees with the company that nCRT is not a valid comparator, as these patients form a smaller subgroup compared to the ITT population in the AEGEAN trial and treatment modalities are different. Whilst the EAG accepts that nCRT may not be routinely given in the scope population, this cannot be automatically inferred to mean that nCRT is inferior to perioperative durvalumab in the scope population, and thus eligible for exclusion. Further details regarding this key issue are discussed in Section 2.3 of this report.

4.2.5 Perspective, time horizon and discounting

The model was developed from a UK healthcare perspective, a lifetime time horizon was used, with a 1-month (i.e., 4.35 weeks) cycle length and half-cycle correction was applied. Discount rates of 3.5% are applied to both costs and benefits.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for the intervention and comparators are the AEGEAN (TP1, TP2 and TP3), PACIFIC (TP4 and TP5), PROCLAIM (TP4), and KEYNOTE (TP6) trials, and data from Wong et al. 2016[29] (TP4, TP5 and TP6), see also CS, Table 31. Additionally, next to the abovementioned trials, relative effectiveness was based on the methods described in CS Section B.2.9.1 and considered in Chapter 3 of the EAG report as well as a meta-analysis by Hung et al. 2019.[30]

- AEGEAN trial (DCO 10 November 2022, mITT population):[13] a phase III RCT comparing neoadjuvant durvalumab in combination with PDC followed by adjuvant durvalumab monotherapy versus neoadjuvant placebo + PDC in stage II-IIIB resectable non-squamous NSCLC.
- PACIFIC trial:[31] a phase III RCT comparing chemoradiotherapy (CRT) followed by durvalumab (as consolidation therapy up to 12 months) versus CRT followed by placebo in stage III NSCLC who did not have disease progression after two or more cycles of platinum-based CRT.
- PROCLAIM:[32] a phase III RCT comparing concurrent pemetrexed-cisplatin with radiotherapy (RT) and etoposide-cisplatin with RT in stage IIIA/B unresectable non-squamous NSCLC investigating etoposide-cisplatin with RT versus pemetrexed-cisplatin with RT.
- KEYNOTE-024:[33] a phase III RCT comparing pembrolizumab and investigator's choice of platinum-based chemotherapy in previously untreated stage IV NSCLC patients with PD-L1 ≥50%.
- KEYNOTE-189:[34, 35] a phase III RCT comparing pembrolizumab with PDC and placebo with PDC in metastatic non-squamous NSCLC previously untreated for metastatic disease.
- KEYNOTE-407:[36, 37] a phase III RCT comparing pembrolizumab with PDC and placebo with PDC in metastatic squamous NSCLC previously untreated for metastatic disease.
- Wong et al. 2016[29]: a study (United States (US)) reporting on characteristics and survival after LRR and DM, stratified based on treatment (active versus BSC), in patients with surgically

resected stage I-III NSCLC that were randomly selected from the National Cancer Data Base in 2006–2007.

Standard parametric survival models were used to estimate transition probabilities. The most appropriate parametric survival models were selected, in line with NICE Decision Support Unit (DSU) guidance, using the following criteria (CS Figure 21):

- Assess the proportional hazards assumption (cumulative hazard plots, smoothed hazards plots and Schoenfeld residuals)
- Assess statistical goodness of fit, i.e. fit to the observed data (Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC))
- Assess visual goodness of fit, i.e. fit to the observed data (visually comparing parametric curves and the KM curves).
- Assess plausibility of the extrapolation based on comparison with external evidence[38, 39]
- Assess plausibility of the extrapolation based on clinical expert opinion (UK Advisory Board[40])

4.2.6.1 Transitions from the event-free health state (TP1, TP2, TP3)

Transition probabilities originating from the EF state were calculated based on EFS from the AEGEAN trial. Subsequently, estimated EFS was used to calculate transition probabilities for: EF to LRR (TP1), EF to DM (TP2), and EF to death (TP3). According to the company both AEGEAN treatment arms (perioperative durvalumab and neoadjuvant PDC) exhibited similar EFS until the 3-month mark, after which a clear and sustained separation in favour of the perioperative durvalumab arm was shown. This separation in curves beyond 3 months aligns with the planned timing of the first RECIST scan post-randomisation, occurring after neoadjuvant therapy completion and prior to surgery. Moreover, data from the neoadjuvant PDC arm of the AEGEAN trial was employed to estimate and extrapolate EFS for neoadjuvant PDC while the EFS for perioperative durvalumab and other comparators were estimated by applying a HR.

4.2.6.1.1 Proportional hazards assumption

CS Section B.2.9.1 and CS Appendix M indicated evidence of non-proportionality based on visually examining the (log cumulative) hazards (with initially increasing hazards and then slowly decreasing hazards over time) as well as the Schoenfeld residuals. However, the Schoenfeld test indicated that the proportional hazards assumption may hold (p=0.411) over the entire trial duration. Moreover, the 3-month time period is a turning point in terms of hazard function and aligns with the planned timing of the first RECIST scan post-randomisation in the AEGEAN trial. Therefore, the company explored a piecewise approach using a 3-month cut-point (91.3 days). According to the company, this approach better accounts for changes in hazards compared to using standard parametric distributions throughout and the proportional hazards assumption holds for the piecewise 3 month + approach (CS Figure 22).

4.2.6.1.2 Fit to the observed data

The AIC and BIC of the log-logistic was lowest while the Weibull, generalised gamma and log-normal are within three points based on the AIC (CS Table 32). Visually, all parametric distributions appear to provide reasonable fits, except for the exponential distribution (CS Figure 24).

4.2.6.1.3 Plausibility of the extrapolation based on comparison with external evidence

The pooled 5-year EFS for neoadjuvant chemotherapy from the NSCLC Collaborative Group meta-analysis (MACG), was estimated to be 36% (CS Table 34). However, according to the company, the credibility of the meta-analyses was uncertain, due to its inclusion of studies conducted in 2007 or before and since it included a substantial proportion (49%) of stage IA-IB patients, who typically exhibit higher EFS rates than individuals in a stage II-IIIB population (AEGEAN trial population). The company stated that (based on clinical opinion) the EFS at 5 years retrieved from the MACG was an underestimation for patients receiving neoadjuvant PDC.

The CS stated that the 5-year EFS predicted for the neoadjuvant PDC arm in AEGEAN by the Weibull model most closely aligns with the committee preferred 5-year EFS in TA876 (CS Table 33).

4.2.6.1.4 Plausibility of the extrapolation based on clinical expert opinion

In a UK clinical Advisory Board, clinicians were provided with EFS data at intervals of 6, 12, 24, 36, 48, and 60 months for the Weibull, log-normal, log-logistic, and generalised gamma models (CS Table 33). 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 38% of patients being event free (EF) at 60 months.

4.2.6.1.5 Base-case approach for EFS

The company adopted a piecewise approach, using the neoadjuvant PDC KM data for the first 3 months (for all treatment strategies), after 3 months the parametric survival model with the log-normal that was determined to be the most appropriate to use in the base-case analysis (KM + log-normal). As external data indicated lower 5-year EFS, scenario analyses were conducted using KM + log-logistic, K- M + generalised gamma and KM + Weibull to estimate and extrapolate EFS.

4.2.6.1.6 Estimating TP1 (EF to LRR) and TP2 (EF to DM)

Due to a low number of events recorded in the AEGEAN trial for EF to LRR (TP1) and EF to DM (TP2), transition probabilities for each individual transition were derived based on the extrapolated EFS data and combined with the proportion of patients experiencing either LRR or DM.

More specifically:

- TP1 (EF → LRR) = probability of EFS event × probability of the event being LRR
- TP2 (EF → DM) = probability of EFS event × probability of the event being DM
- 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 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.

4.2.6.1.7 Estimating TP3 (EF to death)

For the transition from EF to death (TP3), due to the low number of death events as a first EFS event, the AEGEAN data across arms were pooled for TP3 (i.e. TP3 is assumed treatment independent). To estimate time to death as first EFS event, a separate parametric survival model was used by the

company. According to the CS, 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 (CS Figure 29) and it ensured consistency with the EFS extrapolation. T

4.2.6.1.8 Relative effectiveness

The EFS for strategies other than neoadjuvant PDC were estimated by applying a HR to the neoadjuvant PDC EFS from month 3 onwards (Table 4.5). The methods of estimating these HRs is described in CS Section B.2.9.1 and considered in Chapter 3 of the EAG report.

Table 4.5: EFS piecewise (3 + months) HRs

	HR (95% CI)		Method	CS
	Versus neoadjuvant PDC	Versus perioperative durvalumab		
Neoadjuvant PDC			MAIC weighting to CheckMate-816	Section 2.9.1 and Table 35
Perioperative durvalumab			MAIC weighting to CheckMate-816	Section 2.9.1 and Table 35
Neoadjuvant nivolumab + PDC			MAIC weighting to CheckMate-816	Section 2.9.1 and Tables 21, 38
Surgery alone			Random effects NMA	Section 2.9.2 and Table 39 + clarification response Table 19
Adjuvant PDC			Random effects NMA	Section 2.9.2 and Table 39+ clarification response Table 19

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

4.2.6.1.9 Cure assumption

The CS states that several studies have demonstrated that the risk of recurrence peaks in the years immediately after surgery but is considerably reduced by 5 years after surgery.[41-45] Some patients may still experience recurrence beyond 5 years after surgery, but the risk remains low.[46-48] According to the CS, clinical experts across the UK consider patients who remain disease-free 5 years after treatment with curative intent to have a very low risk of recurrence and be functionally cured. Therefore, the company assumed that 95% of patients would achieve cure if they have not experienced an EFS event at 5 years, i.e. assuming that 95% of patients in the EFS health state at 5 years will remain EFS until they die (while TP1, TP2 and TP3 were applied for the remaining 5%). The CS stated that this is consistent with previous NICE appraisals assessing early-stage NSCLC (TA761, TA823 and TA876). Clinicians consulted by the company endorsed the plausibility of cure, deemed the 5-year timeframe appropriate, and agreed that a proportion of 90-95% of patients achieving cure was reasonable.

4.2.6.2 Transitions from the LRR health state (TP4, TP5)

Patients in the LRR health state can either progress to the DM state (TP4) or transition to the death state (TP5). These transitions depended on the specific treatments received in the LRR health state (see Table 4.6). Treatment options in LRR are based on TA761 and include:

- durvalumab + RT + cisplatin + etoposide – PACIFIC and PROCLAIM (PD-L1 ≥1%),
- RT – PACIFIC, PROCLAIM and Hung et al. 2019,[30]
- RT + cisplatin + etoposide – PACIFIC and PROCLAIM,
- BSC – Wong et al. 2016.[29]

It was assumed that the proportion of patients that received BSC in the LRR health state (20.5% based on Wong et al. 2016[29]) could not transit to the DM health state but only to the death state (i.e., TP4 = 0% for the proportion of patients receiving BSC in the LRR health state).

4.2.6.2.1 Estimating TP4 (LRR to DM)

The probability of progressing from the LRR to the DM health state (TP4) was determined from the PACIFIC and PROCLAIM trials, conducted in locally advanced NSCLC.

Given that the timing of randomisation in PACIFIC to either durvalumab or placebo was after patients had received CRT (approximately 2 months), digitised progression-free survival (PFS) data from the PROCLAIM trial (etoposide + cisplatin arm) was used to model the initial period on entry into the LRR health state (i.e., for the duration of CRT). Time to progression (TTP) data from PACIFIC (considered in TA798) was utilised from month 3 onwards. Consistent with the NICE committee preferred extrapolation in TA798, the generalised gamma parametric survival model was adopted. For patients who received RT in LRR, a HR of 1.37 (CS Table 41) was applied to the predicted PFS of CRT using data from the Hung et al. 2019[30] meta-analysis (CRT versus RT) to estimate PFS for RT. It was assumed that the proportion of PFS events categorised as 'progression' (TP4) in each cycle was the same for RT as observed in CRT from the PACIFIC trial.

4.2.6.2.2 Estimating TP5 (LRR to death)

For the transition from LRR to death, a distinction was made between patients that received active treatment (TP5a), and those that received BSC (TP5b).

For TP5a, the transition from LRR to death was informed using UK general population mortality data for the first 2 months. From month 3 onwards, the transitions were informed by pre-progression survival (PrePS) in PACIFIC, which was estimated based on the difference between PFS and TTP extrapolations, consistent with TA798. Consistent with the extrapolation of PACIFIC TTP data (see TP4 above) the generalised gamma was selected for extrapolating the PACIFIC PFS data.

For TP5b, OS post-recurrence data for patients with local recurrence post-resection who received BSC (Wong et al. 2016[29] sourced from the National Cancer Database) was used to estimate the transition from LRR to death. Based on the statistical goodness of fit (CS Table 43) and visual comparison with the KM curves (CS Figure 33), the log-normal provided was selected as the most appropriate for the CS base-case analysis.

4.2.6.3 Transitions from the DM health state (TP6)

From DM, the probability of transitioning to death (TP6) relied on the use of a nested partitioned survival model (PSM). PFS and OS data were used to estimate health state occupancy for progression-free within DM (DM1) and progressed disease (PD) within DM (DM2). DM1 was informed by PFS, whilst DM2 was informed by the difference between OS and PFS (i.e., post-progression survival or PPS). Estimated PFS and OS transitions depended on the specific treatments received in the DM health state. Treatment options in DM include (CS Figure 35):

- pembrolizumab (TA531) – KEYNOTE-024 (PD-L1 ≥50%),
    - PFS: log-logistic distribution
    - OS: log-normal distribution
- atezolizumab (TA705) – equivalent efficacy to pembrolizumab in KEYNOTE-024 (PD-L1 ≥50%) is assumed,
    - PFS: log-logistic distribution
    - OS: log-normal distribution
- pembrolizumab + PDC (TA770 and TA683) – KEYNOTE-407 (squamous) and KEYNOTE-189 (non-squamous),
    - PFS: log-logistic distribution (squamous) and log-normal distribution (non-squamous)
    - OS: log-logistic distribution (both squamous and non-squamous)
- atezolizumab + bevacizumab + PDC (TA584) – equivalent efficacy to pembrolizumab + PDC in KEYNOTE-189 (non-squamous) is assumed,
    - PFS: log-logistic distribution (squamous) and log-normal distribution (non-squamous)
    - OS: log-logistic distribution (both squamous and non-squamous)
- PDC – KEYNOTE-024 (PD-L1 ≥50%), KEYNOTE-407 (squamous) and KEYNOTE-189 (non-squamous),
    - PFS: log-logistic distribution (squamous) and log-normal distribution (non-squamous)
    - OS: log-logistic distribution (both squamous and non-squamous)
- BSC – Wong et al. 2016[29]
    - OS: log-normal distribution

For active treatments (non-BSC), the preferred (non-piecewise) extrapolations used in the original NICE TAs were selected. In cases where a piecewise approach was utilised, the curves with the best statistical fits, as determined by AIC/BIC, were selected (CS Appendix M). The selection of data from these trials and the adoption of preferred extrapolations were carefully selected to be consistent with previous NICE TAs (CS Table 45).

As per LRR, patients receiving BSC in DM1 could only transition directly to the death health state (i.e., the transition from DM1 to DM2 was assumed 0% for the proportion of patients receiving BSC in the DM1 health state). For the OS extrapolation for BSC from Wong et al. 2016, the log-normal distribution was selected because it had the best statistical fit and provided a good visual fit to the observed data.

4.2.6.4 Weighted PFS and OS in the LRR and DM health states

The transition probabilities in the LRR and DM health states were dependent on treatments administered upon entering these health states (see Table 4.6). This was based on a weighted average using the treatment distributions assigned for LRR and DM1. The distribution of treatments in the perioperative durvalumab arm and neoadjuvant nivolumab + PDC arm differs depending on whether patients were retreated with IO or not. The company assumed, in line with TA823 and TA876, to be retreated with IO (i.e., pembrolizumab/atezolizumab monotherapies or combination therapies) patients should not have progressed within 6 months after completion of durvalumab or nivolumab treatment in the EF health state, i.e., after 21 months for perioperative durvalumab and after 8 months for neoadjuvant nivolumab + PDC. Therefore, in the model, for all patients who received perioperative durvalumab in the EF health state and entered the LRR or DM health state before month, no IO retreatment was permitted, whereas IO retreatment was permitted for patients who entered the LRR or DM health state in subsequent months.

Table 4.6: Distribution of treatments in the LRR and DM health states

	Including IO (re)treatment	**Not including IO (re)treatment**	**Source/assumption**
LRR health state (based on "Tx Shares & Costs" worksheet)			
Durvalumab + RT + cisplatin + etoposide	37.1%	0.0%	Assumes 70% will receive IO if IO permitted and PD-L1 ≥1%.
RT	34.8%	65.2%	Consistent with TA761 (based on UK clinical expert opinion), it was assumed that (of those patients that do not receive IO or BSC), 82% RT and 18% CRT.
RT + cisplatin + etoposide	7.6%	14.3%	
BSC	20.5%	20.5%	Wong et al. 2016.
DM1 health state (based on "Tx Shares & Costs" worksheet)			
Pembrolizumab	15.7%	0.0%	Assumes 80% will receive IO if IO permitted. Exact treatment depending on PD-L1 ≥50%, histology (non-squamous/squamous) and market shares for pembrolizumab/atezolizumab (based on IPSOS).
Pembrolizumab + carboplatin + pemetrexed (non-squamous)	17.5%	0.0%	
Pembrolizumab + carboplatin + paclitaxel (squamous)	21.6%	0.0%	
Atezolizumab	2.4%	0.0%	
Atezolizumab + bevacizumab + carboplatin +	4.7%	0.0%	

	Including IO (re)treatment	Not including IO (re)treatment	Source/assumption
paclitaxel (non-squamous)			
Carboplatin + pemetrexed (non-squamous)	7.8%	39.2%	
Carboplatin + paclitaxel (squamous)	7.6%	38.1%	
BSC	22.7%	22.7%	Wong 2016 et al.
DM2 health state (based on "Tx Shares & Costs" worksheet)			
Atezolizumab	0.0%	11.1%	Assume IO in DM2 with PD only for patients who received active therapy, but did not receive IO in DM1
Docetaxel + nintedanib	55.4%	44.3%	Those not receiving IO nor BSC
BMS	44.6%	44.6%	KEYNOTE trials
BSC = best supportive care; CRT = chemoradiotherapy; DM = distant metastases; IO = immuno-oncology; LRR = locoregional recurrence; PD = progressed disease; PD-L1 = programmed cell death ligand-1; RT = radiotherapy; TA = Technology Appraisal; Tx = treatment; UK = United Kingdom			

EAG comment: The main concerns of the EAG relate to: a) the estimation of the EFS HRs; b) assuming the EFS HRs are constant over time; c) estimation of transitions from the EFS health state (TPs1-3); d) relative effectiveness of IO retreatment; e) estimation of EFS and; f) parametric model selections for the LRR DM states (TP4-6).

a) The HRs versus neoadjuvant PDC for 3+ months were based on the 'base-case' MAIC weighting to CheckMate 816 for perioperative durvalumab as well as neoadjuvant nivolumab + PDC while for adjuvant PDC and surgery alone the HRs versus neoadjuvant PDC for 3+ were based on sensitivity analysis 2 (excluding two studies from the network) of the random effects NMA (see also CS Section 2.9). The CS stated that the "*results of sensitivity analysis 2 were associated with greater precision (narrower 95% CrIs) and as a result of excluding Rosell 1994 and Li 2009, statistical heterogeneity (I^2) was reduced from* [redacted] *in the base case analysis to* [redacted]". The EAG believes the CS approach to estimate HR is reasonable (see also Chapter 3 of this report), with the caveats i) that the HRs are based on two separate analyses (MAIC and NMA) and ii) no time-varying HR approach was explored by the company in response to CQs A24 and B9.
b) The EFS HRs are assumed to be maintained after the observed data period from the AEGEAN trial. The company argued in response to CQ B9 that "*The use of IO therapy in the neoadjuvant setting has the advantage of priming the patient's immune system whilst the tumour and any involved lymph nodes are still present prior to surgery. Following resection, continuation of immuno-oncology therapy in the adjuvant setting (as per the perioperative approach) may be beneficial, to consolidate the immune response and suppress/eradicate micrometastases, and thus potentially delay or prevent disease recurrence.*" … "*In TA876, clinicians validated the EFS long-term projections (modelled by a constant HR) for neoadjuvant nivolumab + PDC*

and neoadjuvant PDC." The EAG believes that it is reasonable that part of the relative treatment effect is maintained after the observed data period from the AEGEAN trial. However, whether a constant HR should be maintained indefinitely (or until 'cured') is uncertain. The EAG explored the impact of treatment effect waning in a scenario analysis, adopting a 5-year time horizon (acknowledging this is a crude way to explore this impact in the absence of any appropriate scenario analyses provided by the company in response to CQ B9e).

c) Transition probabilities originating from the EF state were calculated based on EFS from the AEGEAN trial. Subsequently, estimated EFS was used to calculate transition probabilities for: EF to LRR (TP1), EF to DM (TP2), and EF to death (TP3). Additional explanation is provided regarding to the calculation of TP1-3 in response to CQ B10. The EAG believes the approach adopted by the company is in general reasonable. However, the probability of the event being LRR or DM was assumed to be constant over time as well as equal for all treatments (i.e. time and treatment independent). This is inconsistent with clinical expert opinion obtained by the EAG. Moreover, the company acknowledged the potential treatment dependence of LRR or DM probabilities. Nevertheless, the company did not provide the analyses requested in CQ B10 to explore the potential implications of this assumption.

d) Immuno-oncology (IO) retreatment was allowed in the economic model. It is uncertain whether the relative effectiveness of initial IO treatment and IO retreatment would be similar or whether the relative effectiveness of IO retreatment would be diminished compared with initial IO treatment. In response to CQ B13, the company acknowledged that "*the model implicitly assumes that the efficacy of IO in these health states (for those patients who are eligible to receive IO) is the same, regardless of whether IO was received in the previous health state*". The company did however not provide the analyses requested in CQ B14 (i.e. assuming that post-recurrence, the relative effectiveness of IO retreatment would be diminished compared with initial IO treatment) to explore the impact of this assumption.

e) According to the CS "*The hazard plots' shape favoured adopting piecewise extrapolations from 3 months onward to account for changes in hazards. As can also be seen from the cumulative hazard and smoothed hazard plots specifically, the 3-month time period is a turning point in terms of hazard function and aligns with the planned timing of the first RECIST scan post-randomisation in the AEGEAN trial. To capture changes pre- versus post-surgical assessments, a piecewise extrapolation using a 3-month cut-point (91.3 days) was explored. This approach better accounts for these changes in hazards compared to using standard parametric distributions throughout, as demonstrated in the extrapolated EFS over the trial duration in Appendix M. A*" The EAG agrees (based on CS Appendix M) that the smoothed hazard plots indicate a turning point in terms of hazard function. However, given that this turning point aligns with the planned timing of the first RECIST scan post-randomisation in the AEGEAN trial, it is likely protocol driven and it is questionable whether using a piecewise model (with a KM curve for the first 3 months) results into overfitting to the trial data. The standard parametric models (CS Appendix Figure 22), with a smoother EFS curve that appears less protocol driven, might be a better reflection of clinical practice in England and Wales. In response to CQ B11 the company further justified the appropriateness of a piecewise model with a 3-month turning point by stating that: "*because patients undergo surgery following the completion of 4 cycles of neoadjuvant treatment—equivalent to approximately 3 months for both treatment options … In clinical practice it is expected that patients would be assessed for disease progression prior to surgery. If not, the identification of disease progression would likely occur during attempted surgery. Therefore, a turning point at or around the time of surgery is also expected in clinical*

practice." The EAG believes this approach is reasonable. Moreover, the EAG obtained clinical expert opinion to validate the 5-year and 10-year EFS, the clinical expert indicated that these were within the ranges that are considered clinically plausible.

f) To inform the parametric model selections for the LRR DM states (TP4-6), not all criteria (mentioned above in Section 4.2.6) were considered/reported in the CS, i.e. no complete assessment was reported. This seemed predominantly to be informed by the fit to the observed data (e.g. AIC/BIC). To EAG assessed to what degree alternative parametric distributions did maximally increase the incremental cost-effectiveness ratio (ICER). For TP4, TP5a and TP5b the ICER increased with a maximum of [redacted]. While for TP6, the PFS ([redacted]) and OS ([redacted]) parametric distributions for the pembrolizumab treatment options did mainly impact the results. While individually the impact might not be substantial, when combined the impact might be substantial. Hence, it would be informative to have further information (on all criteria) justifying the parametric model selections for TP4-6.

4.2.7 AEs

The main source of evidence used to inform treatment AEs for intervention and comparators is the AEGEAN trial (CS Tables 24 and 25). The company's initial cost effectiveness model included adverse reactions resulting from grade 3 or 4 AEs which occurred in more than 5% of patients during the neoadjuvant and/or adjuvant treatment phases in the AEGEAN trial. In response to the clarification letter, the company updated their base-case and economic model by including grade 3 or 4 AEs which occurred in more than 1% of patients. AE rates were assumed to be 0% for the surgery alone arm, in line with TA 876. AE rates for adjuvant PDC were assumed to be the same as for neoadjuvant PDC (Table 4.7).

Table 4.7: AE frequencies, costs, and disutilities

	AE	Number of events (%)	Disutility	Total QALY loss (one-off)	Unit costs	Total AE cost (one-off)
Perioperative durvalumab	Neutropenia	8.7%	-0.007	-0.002	£1,366	£387
	Neutrophil count decreased	9.5%	-0.007		£1,366	
	Anaemia	4.5%	-0.007		£537	
	Leukopenia	2.2%	-0.007		£1,366	
	White blood cell count decreased	2.0%	-0.007		£1,366	
	Platelet count decreased	1.7%	-0.007		£1,366	
	Thrombocytopenia	1.5%	-0.007		£1,366	
	Vomiting	0.7%	-0.004		£1,261	
	Asthenia	0.0%	-0.006		£770	
	Decreased appetite	0.0%	-0.004		£77	

	AE	Number of events (%)	Disutility	Total QALY loss (one-off)	Unit costs	Total AE cost (one-off)
Neoadjuvant nivolumab + PDC	Neutropenia	8.5%	-0.007	-0.002	£1,366	£320
	Neutrophil count decreased	7.4%	-0.007		£1,366	
	Anaemia	2.8%	-0.007		£537	
	Leukopenia	1.7%	-0.007		£1,366	
	White blood cell count decreased	0.0%	-0.007		£1,366	
	Platelet count decreased	0.0%	-0.007		£1,366	
	Thrombocytopenia	2.3%	-0.007		£1,366	
	Vomiting	2.2%	-0.004		£1,261	
	Asthenia	0.6%	-0.006		£770	
	Decreased appetite	1.1%	-0.004		£77	
Neoadjuvant PDC	Neutropenia	8.8%	-0.007	-0.003	£1,366	£473
	Neutrophil count decreased	10.6%	-0.007		£1,366	
	Anaemia	5.0%	-0.007		£537	
	Leukopenia	3.0%	-0.007		£1,366	
	White blood cell count decreased	3.0%	-0.007		£1,366	
	Platelet count decreased	3.3%	-0.007		£1,366	
	Thrombocytopenia	2.3%	-0.007		£1,366	
	Vomiting	1.0%	-0.004		£1,261	
	Asthenia	1.3%	-0.006		£770	
	Decreased appetite	0.3%	-0.004		£77	

Based on NHS Reference Costs 2021/22; AEGEAN; TA876 (Nafees et al. 2018)
AE = adverse event; NHS = National Health Service; PDC = platinum-doublet chemotherapy; QALY = quality-adjusted life year; TA = Technology Appraisal

EAG comment: The main concerns of the EAG relate to: a) modelling of grade 3 or 4 AEs only if they occurred in more than 5% of patients in the AEGEAN trial, b) assumptions related to the reversibility and duration of the modelled AEs, c) the assumption of 0% surgery-related grade 3+ AEs, and d) AE-related error fixes in the economic model.

a) The company modelled grade 3 or 4 AEs which occurred in more than 5% of patients during the neoadjuvant and/or adjuvant treatment phases in the AEGEAN trial. In its clarification letter, the EAG requested an updated economic model and scenario analysis including all grade 3+ AEs that occurred during the neoadjuvant and/or adjuvant treatment phases in the AEGEAN trial, regardless of the percentage of patients in which these occurred. In their response, the company provided an updated economic model including grade 3 or 4 AEs which occurred in

more than 1% (instead of 5%) of patients, arguing that the inclusion of all grade 3+ AEs in AEGEAN (and comparator trials for non-AEGEAN comparators) would lead to a great number of additional AEs, which would overcomplicate the model and the assumptions required for costs and disutilities related to AEs. The company's updated economic model resulted in the addition of seven AEs (leukopenia, white blood cell count decreased, platelet count decreased, thrombocytopenia, vomiting, asthenia and decreased appetite) to the initially included neutropenia, neutrophil count decreased and anaemia. Additionally, the frequency of neutropenia in the durvalumab arm was increased from 8.7% to 9.0% to exactly align with Heymach et al. 2023.[14] The company further stated that including AEs of grade 3-4 that occurred in >1% of patients is a conservative approach that would only have a small impact on the results. The EAG agrees on this and adopted the company's updated approach (including AEs of grade 3-4 that occurred in >1% of patients) in its base-case.

b) The company applied AE costs and disutilities as a one-off cost/disutility in the first cycle of the economic model. The EAG requested the company to comment on the reversibility and duration of the modelled AEs and to justify their assumption of a 1-month duration (i.e. one model cycle) for all AEs irrespective of treatment. In response to the clarification letter, the company stated that there are no available data from the AEGEAN trial regarding the duration of AEs, and thus, for simplicity, a duration of 1 month was assumed. The company further noted that, although this was considered a limitation of the economic model, the impact of this limitation was expected to be minor. The EAGs clinical expert expected that almost all of the modelled AEs would be fully reversible but noted that anaemia is more difficult to define as it can be cumulative throughout the course of treatment. Considering all of the above, the EAG agrees with the company's simplified assumption of a 1 month AE duration.
c) As per TA876[38], surgery-related grade 3+ AEs were assumed to be 0%. In response to the clarification letter, while recognising this being a strong assumption, the company suggested that this approach is conservative. The EAG agrees that the assumption of no surgery-related AEs is a strong assumption given the possible complications that may arise during surgery. Although the economic model is likely underestimating additional costs and disutilities associated with AEs from surgery, the EAG agrees that the company's assumption is likely conservative.
d) In response to the clarification letter, the company fixed two errors related to AEs its economic model: 1) a typo in the CHOOSE formula in the number of AEs for the selected comparator and 2) the calculation of QALY loss divided the time duration of AEs by the number of days in a week rather than days in a cycle. The EAG agrees on both error fixes.

4.2.8 HRQoL

The utility values were estimated for the following health states: EF, LRR, DM1 and DM2.

The HRQoL data from the AEGEAN trial was used to inform the EF health state utility. The HRQoL was assessed in the AEGEAN trial using the EQ-5D-5L at baseline; at each treatment visit during the neoadjuvant treatment period (i.e., weeks 0, 3, 6, and 9); at pre-surgical assessment (within 30 days of surgery); at the first treatment visit during the adjuvant treatment period; 30 days (±3 days) after the last dose of study treatment; and at months 2, 3 and 6 (±1 week) after the last dose of study treatment following completion or discontinuation of study treatment.

The EQ-5D-5L responses from the mITT analysis set of AEGEAN (i.e., excluding EQ-5D-5L observations with any missing domain responses) were mapped to EQ-5D-3L values using the

Hernández Alava et al. 2017[49] algorithm. A mixed model for repeated measures (MMRM), including recurrence status as a covariate, was used to estimate the EF health state utility.

Due to limited follow-up data in the AEGEAN trial, alternative sources and assumptions were used to inform subsequent health state utilities. For the LRR health state, utilities were sourced from TA798[50], which were derived using EQ-5D data from the PACIFIC trial (patients with unresectable, stage III NSCLC whose disease had not progressed after platinum-based concurrent CRT)[31]. Utility values for the DM health states were sourced from TA683[51], which were derived using EQ-5D data from the KEYNOTE-189 trial (patients with previously untreated metastatic non-squamous NSCLC without sensitising EGFR or ALK mutations).[35]

4.2.8.1 HRQoL data identified in the review

According to the CS, the SLR identified nine studies and nine HTA submission reporting relevant utility values. Out of these, utilities from previous HTA submissions were utilised in the economic model for the DM health state (TA683) as well as for AE disutilities (TA876).[38, 51]

4.2.8.2 HSUVs

A summary of all utility values used in the cost effectiveness analysis is provided in Table 4.8.

Table 4.8: HSUVs

Health state	Utility value	SE	Reference
EF	[redacted]	[redacted]	AEGEAN[14]
LRR	[redacted]	[redacted]	TA798 (PACIFIC trial)[31]
DM1	0.759	0.076	TA683 (KEYNOTE-189 trial)[51]
DM2	0.662	0.066	TA683 (KEYNOTE-189 trial)[51]

Based on CS Table 49[3]
CS = company submission; DM = distant metastases; EF = event free; HSUV = health state utility values; LRR = locoregional recurrence; SE = standard error; TA = Technology Appraisal

4.2.8.3 Disutility values

Disutilities associated with AEs were modelled to capture the decline in patients' HRQoL caused by treatment-related adverse events (TRAEs). As HRQoL decrements due to AEs were not available from AEGEAN, disutilities were sourced from Nafees et al.[52] (EQ-5D measured in metastatic NSCLC), in line with in TA876.[38]

The company determined the total mean QALY loss associated with AEs for each treatment by calculating the treatment-specific AE frequencies, the mean utility decrements related to these AEs, and the mean AE duration of each. It was assumed that TRAEs are most likely to occur shortly after initiating a new therapy and hence disutilities were applied in the first model cycle only.

The AE disutilities values applied in the cost effectiveness model are presented in CS Table 51.

EAG comment: The main concerns of the EAG relate to: a) the estimation of the EF utility, b) the relatively small utility decrement from EF to LRR, c) the KEYNOTE-189 trial to inform the DM1 and DM2 health state utilities, and d) implementation and source of utility decrements associated with AEs.

a) HRQoL data collected in the AEGEAN trial were analysed using MMRM to estimate the EF health state utility in the economic model. The EAG's concerns relate to 1) the EF utility was informed by the neoadjuvant period of the AEGEAN trial only (i.e. data from the adjuvant period were not used), 2) the EF utility in the company's base-case was higher than the age-adjusted UK general population utility, and 3) missing HRQoL data in the AEGEAN trial.
    i. The company estimated the utility value for the EF health state based on the neoadjuvant period of the AEGEAN trial only (i.e. data from the adjuvant period were not used). In response to the clarification letter, the company mentioned the potential implications of not using data from the adjuvant period of the AEGEAN trial, including a limited representation of overall HRQoL, potential oversight of the varying observed effects at different points in time, and the risk of underestimating or overestimating the treatment's impact. The company argued that data from the adjuvant period were not used due to collection limitations, as HRQoL data were only gathered during the adjuvant baseline visit and the post-discontinuation follow-up visit, excluding the rest of the adjuvant treatment visits. The EAG considers the estimation of the EF utility based on the neoadjuvant period of the AEGEAN trial only to be questionable and is concerned about the potential implications as highlighted by the company in its clarification response.
    ii. The EF utility in the company's base-case ([redacted]) was higher than the age-adjusted UK general population utility. A scenario analysis was provided by the company in which the EF utility was capped to the Health Survey for England 2014[53] based age-adjusted general population norms (0.829). The EAG questions the face validity of a higher EF utility value than the general population in a diseased population in the company's base-case and hence capped the EF utility in the EAG base-case to the age-adjusted UK general population norms.
    iii. The company fitted an MMRM to estimate the EF health state utility in the economic model and assumed missing HRQoL data to be missing at random. Although the EAG agrees that this assumption is appropriate if the MMRM is correctly specified, it noted that the percentage of missing HRQoL data in the AEGEAN trial was substantial ([redacted] at week 6 and further increased thereafter). In its clarification letter, the EAG requested the likely causes of missing data and what the potential impact of these missing data would be on the estimation of the EF utility. The company acknowledged the potential limitations due to missing data but responded that providing a definitive assessment of the impact of missing HRQoL data is challenging. The EAG is concerned that the current EF utility may be overestimated if the missing data predominantly included patients with worse HRQoL. The company explored a scenario analysis using a lower EF utility from Andreas et al.[54] (0.72), which had a substantial impact on the ICER (24% increase). Although the EAG appreciates the company's attempt of getting insights into the potential impact of lower utility values on the cost effectiveness results, it noted that the other health state utilities in this scenario analysis were not adjusted relative to the EF utility, which resulted in the LRR and DM1 utilities being higher than the EF utility.

b) The utility values for the EF and LRR health states in the company's base-case were respectively [redacted] and [redacted]. The EAG considers the utility decrement ([redacted]) from EF to LRR to be relatively small and noted that the EAGs clinical expert in TA876 estimated this utility difference to be 0.15-0.20.

[redacted], which the EAG considers questionable. Therefore, the EAG explored a scenario analysis using the age-adjusted general population utility for the EF health state (as in EAG base-case) and apply a 0.2 utility decrement from EF to LRR in line with clinical advice from TA876. The EAG also adjusted the DM1 and DM2 utilities to maintain the absolute increment from LRR to DM1 and LRR to DM2.

c) The company informed the DM1 and DM2 HSUV in their economic model based on the KEYNOTE-189 trial. The EAG's clinical expert, however, noted that almost a third of patients in the DM1 and DM2 health states would not be receiving treatment that was given in KEYNOTE-189 (immunotherapy + chemotherapy) as they would receive immunotherapy alone. The EAG's clinical expert continued that utility values for patients only receiving immunotherapy in the DM1 and DM2 health states therefore may be slightly higher to those who were also receiving chemotherapy. The EAG expects that the impact of this on the cost effectiveness results, however, is likely minor.

d) The company modelled utility decrements associated with AEs based on a study by Nafees et al. 2008.[52] Utility decrements for decreased neutrophil counts and anaemia were assumed to be the same as the utility decrement for neutropenia (-0.08973). However, in the company's model, the reported decrement of -0.08973 was divided by the number of model cycles per year (i.e. 12), resulting in a modelled disutility of -0.007. It is unclear to the EAG why the company did this and considers this to be a modelling error. The EAG fixed this error in its EAG base-case by directly applying the -0.08973 utility decrement from Nafees et al. 2008 to the proportion of patients experiencing the AE for a duration of one model cycle.
Additionally, the EAG noted that there is a more recent study by Nafees et al. 2017[55] which could have been used by the company to inform utility decrements associated with AEs in its economic model. The Nafees et al. 2017 study used the time-trade-off (TTO) valuation method to determine utility scores, whereas the Nafees et al. 2008 used the standard gamble. The EAG notes that, compared to the standard gamble, the TTO valuation method to determine decrements associated with AEs may better align with the EQ-5D (also based on TTO valuation) that was used to estimate the HSUVs. The EAG, however, did not explore this in a scenario analysis as it is expected to have a minimal impact on the cos -effectiveness results.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, treatment administration, RT, surgery, treatment monitoring, supportive care, terminal care, and costs of managing AEs.

Unit prices were based on the National Health Service (NHS) reference prices for 2021/22, British National Formulary (BNF) 2023, electronic market information tool (eMIT), and Personal Social Services Research Unit (PSSRU).

4.2.9.1 Resource use and costs data identified in the review

A de novo SLR was conducted to identify resource use and costs evidence in resectable stage I-III NSCLC. In total, 30 studies were identified, reporting direct resource use (n=30), surgery type (n=14), hospitalisation data (n=13), adjuvant treatment patterns (n=10), and neoadjuvant treatment patterns (n=4). Seven studies reported cost data. Two studies reported UK-specific results.[56] [57]

None of the studies prioritised for data extraction appear to be used to inform healthcare resource use and costs in the CS model, nor used to validate costs used within the economic model. Whilst CS

Appendix I Table 74 provides a brief comment regarding the potential applicability of each included study for global cost effectiveness evaluation, no justification for not utilising study results to inform resource use and costs is provided.

4.2.9.2 Treatment costs (with PAS)

Treatment and administration costs were treatment and health state dependent. An overview of treatment and administration costs are presented for each health state in Table 4.6.

4.2.9.2.1 Drug acquisition costs

Treatment acquisition costs are dependent on dosing regimens and the frequency of administrations, which differ in the adjuvant and neoadjuvant settings.

Acquisition costs in the neoadjuvant and adjuvant settings were calculated based on the time to discontinuation of treatment (TDT) from AEGEAN for all therapies. For outside trial comparators, assumptions were made to model TDT. An overview of these assumptions for the neoadjuvant and adjuvant settings are provided in Table 4.9.

Table 4.9: Overview of assumptions used to inform TDT in the neoadjuvant and adjuvant settings

Treatment arm	Acquisition cost	TDT assumption
Neoadjuvant setting		
Perioperative durvalumab + PDC	Durvalumab cost	Directly from AEGEAN mITT population KM analysis (durvalumab TDT in perioperative durvalumab arm)
	PDC cost	Directly from AEGEAN mITT population KM analysis (neoadjuvant PDC TDT in perioperative durvalumab arm)
Neoadjuvant PDC	PDC cost	Directly from AEGEAN mITT population KM analysis (neoadjuvant PDC TDT in perioperative placebo arm)
Neoadjuvant nivolumab + PDC	Nivolumab cost	Directly from AEGEAN mITT population KM analysis (durvalumab TDT in perioperative durvalumab arm)
	PDC cost	Directly from AEGEAN mITT population KM analysis (neoadjuvant PDC TDT in perioperative durvalumab arm)
Adjuvant setting		
Perioperative durvalumab	Durvalumab cost	Directly from AEGEAN mITT population KM analysis (durvalumab TDT in perioperative durvalumab arm)
Neoadjuvant nivolumab + PDC	PDC cost	Directly from AEGEAN mITT population KM analysis (neoadjuvant PDC TDT in perioperative placebo arm) Adjuvant PDC applied to a proportion assumed to receive adjuvant treatment, based on TA876
Adjuvant PDC	PDC cost	Directly from AEGEAN mITT population KM analysis (neoadjuvant PDC TDT in perioperative placebo arm)

Based on CS Tables 55 and 58[3]

CS = company submission; PDC = platinum-doublet chemotherapy; KM = Kaplan-Meier; mITT = modified intention to treat; TA = Technology Appraisal; TDT = time to discontinuation of treatment

The distribution of PDC types, separated by treatment arm, are displayed in Table 4.10 for the neoadjuvant and adjuvant settings. Neoadjuvant PDC distributions were informed by AEGEAN mITT data for the perioperative durvalumab + PDC and neoadjuvant PDC arms, and by CheckMate 816 for the neoadjuvant nivolumab + PDC arm (considering non-squamous and squamous histology). Adjuvant PDC distributions were informed by TA876 for the neoadjuvant nivolumab + PDC arm and were assumed equally split for the adjuvant PDC arm.

Table 4.10: Distribution of PDC types per treatment arm

PDC types		Neoadjuvant setting			Adjuvant setting	
		Perioperative durvalumab + PDC	Neoadjuvant PDC	Neoadjuvant nivolumab + PDC	Neoadjuvant nivolumab + PDC	Adjuvant PDC
Cisplatin+	Pemetrexed	15.7%	15.1%	39.6%	10.7%	11.1%
	Paclitaxel	0.0%	0.3%	0.0%	-	-
	Vinorelbine	-	-	-	10.7%	11.1%
	Gemcitabine	11.5%	10.8%	38.6%	10.7%	11.1%
	Docetaxel	0.0%	0.0%	0.0%	10.7%	11.1%
Carboplatin+	Pemetrexed	39.4%	36.7%	0.0%	31.5%	11.1%
	Paclitaxel	30.7%	34.9%	21.8%	0.0%	11.1%
	Gemcitabine	2.7%	10.8%	0.0%	0.0%	11.1%
	Vinorelbine	0.0%	0.0%	0.0%	0.0%	11.1%
	Docetaxel	0.0%	0.0%	0.0%	0.0%	11.1%

Based on CS Tables 54 and 57[3]
CS = company submission; PDC = platinum-doublet chemotherapy

Drug dose regimens per model cycle are calculated for the intervention and comparators based on the dose per administration, the number of administrations per treatment cycle, and the duration of treatment cycle for each therapy, and were subsequently adjusted to model cycle length. Average doses for IV interventions were calculated using body surface area (BSA), as calculated using AEGEAN mITT patient characteristics and the formula from Gehan and George.[58] Vial-sharing was assumed to occur with wastage costs thus excluded. No correction was applied for missed doses. Unit treatment acquisition costs were sourced from BNF and eMIT databases and are presented in CS Table 61.

Subsequent treatment distributions in LRR and DM health states are dependent on whether the patient received an IO in the EF health state, and IO retreatment restrictions (i.e., patients that received IO in EF health state but progressed within 6 months after the last dose of IO cannot receive IO in LRR or DM). Patient distributions and treatment shares for LRR and DM are presented in Table 4.5 in Section 4.2.6.

4.2.9.2.2 Drug administration costs

Treatment administration costs were applied per administration for drugs given IV. Unit administration costs were derived from NHS Reference Costs 2021/22, with a cost of £207.59 being applied for simple chemotherapies and £440.71 for complex chemotherapies in the first treatment cycle, and a cost of £326.46 being applied for all subsequent cycles.

No administration costs were assumed for oral therapies, in line with TA823 and TA347.

4.2.9.2.3 RT

Unit costs for RT administration were sourced from NHS Reference Costs 2021/22. A differentiation was made for RT administration costs for RT as part of post-operative CRT, and RT as a treatment option in the LRR health state. Resource use (RT preparations and RT fractions) was derived from Pless et al.[7] for RT as a post-operative treatment, and from NICE NG122 for RT in the LRR state. An overview of RT cost inputs is presented in CS Table 62.

4.2.9.2.4 Surgery

Surgery was divided into thoracotomy and minimally invasive surgery and weighted to derive an estimation for surgery costs. The proportion of patients undergoing surgery was 81% for neoadjuvant durvalumab or after neoadjuvant PDC, as derived from AEGEAN, and 83% after neoadjuvant nivolumab + PDC, as informed by CheckMate 816. All patients receiving surgery alone or adjuvant PDC were assumed to receive the cost of surgery. Surgery type distribution was derived from AEGEAN, with the same distribution for perioperative durvalumab being assumed for neoadjuvant nivolumab + PDC. Further, for patients receiving surgery alone or adjuvant PDC, the same distribution as neoadjuvant PDC was assumed. Surgery cost inputs are presented in CS Table 63.

Table 4.11: Treatment costs per model cycle (monthly)

Treatment		Administration costs	Treatment costs per cycle	Treatment duration (months)
EF health state (informed by "Tx Shares & Costs" worksheet)				
	Neoadjuvant durvalumab	[redacted]	[redacted]	2.8
	Neoadjuvant PDC		[redacted]	2.8

Treatment		Administration costs	Treatment costs per cycle	Treatment duration (months)
Perioperative durvalumab + PDC	Surgery		£7,632	Once only
	Adjuvant durvalumab	[redacted]	[redacted]	11.0
Neoadjuvant PDC	Neoadjuvant PDC	[redacted]	[redacted]	2.8
	Surgery	£0	£7,668	Once only
Neoadjuvant nivolumab + PDC	Neoadjuvant nivolumab	£567	£5,724	2.1
	Neoadjuvant PDC	£0	£115	2.1
	Surgery	£0	£7,632	Once only
	Adjuvant PDC	£372	£59	2.1
	RT	£0	£2,721	1
Surgery alone	Surgery	£0	£7,768	Once only
Adjuvant PDC	Adjuvant PDC	£560	£91	2.1
	Surgery	£0	£7,768	Once only
LRR health state (informed by "Tx Shares & Costs" worksheet)				
Durvalumab + RT + cisplatin + etoposide	Durvalumab	[redacted]	[redacted]	12.0
	RT	£0	£6,891	1.4
	Cisplatin + etoposide	£441	£13	1.8
RT + cisplatin + etoposide	RT	£0	£6,891	1.4
	Cisplatin + etoposide	£441	£13	1.8
RT	RT	£0	£6,891	1.4
BSC	BSC	£0	£0	-
DM1 health state (informed by "Tx Shares & Costs" worksheet)				
Pembrolizumab		£208	£7,624	24.1
Pembrolizumab + carboplatin + pemetrexed (non-squamous)	Pembrolizumab	£208	£7,624	24.1
	Carboplatin	£0	£26	2.8
	Pemetrexed	£0	£78	24.1
Pembrolizumab + carboplatin + paclitaxel (squamous)	Pembrolizumab	£208	£7,624	24.1
	Carboplatin	£0	£31	2.8
	Paclitaxel	£653	£93	2.8
Atezolizumab		£208	£5,519	432.0
Atezolizumab + bevacizumab + carboplatin + paclitaxel (non-squamous)	Atezolizumab	£208	£5,519	432.0
	Bevacizumab	£0	£3,148	432.0
	Carboplatin	£441	£26	2.8
	Paclitaxel	£653	£93	2.8
Carboplatin + pemetrexed (non-squamous)	Carboplatin	£441	£26	2.8
	Pemetrexed	£653	£93	24.1

Treatment		Administration costs	Treatment costs per cycle	Treatment duration (months)
Carboplatin + paclitaxel (squamous)	Carboplatin	£441	£31	2.8
	Paclitaxel	£653	£93	2.8
BSC		£0	£0	-
DM2 health state (informed by "Tx Shares & Costs" worksheet)				
Atezolizumab		£208	£5,519	432.0
Docetaxel + nintedanib		£208	£2,202	432.0
BSC		£0	£0	-
BSC = best supportive care; DM = distant metastases; EF = event free; LRR = locoregional recurrence; PDC = platinum-doublet chemotherapy; Tx = treatment				

4.2.9.3 Health state costs

Health state costs encompass treatment monitoring and healthcare resource utilisation (HCRU) costs and are treatment independent.

4.2.9.3.1 Treatment monitoring

Monitoring costs were included for liver function tests, renal function tests, and complete blood counts and applied to all patients receiving treatment in each model cycle, assuming treatment independence. Unit costs were sourced from NHS Reference Costs 2021/22. One of each test per treatment cycle was assumed for the EF health state, and four per treatment cycle for the LRR health state, based on key opinion leader validation in TA876. The number of tests per treatment cycle for the DM health states were assumed to be the same as LRR. Total monitoring costs were £8.78 for EF, and £35.15 for LRR and DM.

4.2.9.3.2 Healthcare resource use

In the CS, HCRU encompassed clinical visits, hospitalisations, and imaging, and was sourced for each model health state from the LuCaBIS study[54], in line with TA761. The UK-specific data from the study for each health state were adjusted by the time spent in each health state to calculate average HCRU per model cycle. Unit costs for HCRU were sourced form NHS Reference Costs 2021/22. HCRU, unit costs, and total costs can be found in CS Tables 77, 78, and 79, respectively. An overview of total HCRU costs per cycle per health state are provided in Table 4.12.

Table 4.12: Health state costs

Health state	Costs (per cycle)		
	Monitoring	HCRU	Total
EF	£8.78	[redacted]	[redacted]
LRR	£35.15	[redacted]	[redacted]
DM1	£35.15	[redacted]	[redacted]
DM2	£35.15	[redacted]	[redacted]

Health state	Costs (per cycle)		
	Monitoring	HCRU	Total
DM = distant metastases; EF = event free; HCRU = healthcare resource utilisation; LRR = locoregional recurrence			

4.2.9.4 Event costs

A one-off terminal care cost was applied to all patients in the model upon transition to the death health state. This was calculated based on the proportion of patients that received end of life care in a hospital, hospice, or at home, sourced from Brown et al.[59] Unit costs were derived from NHS Reference Costs 2021/22, the PSSRU 2019, and a Marie Curie report. Unit terminal care costs (proportion of patients that died per setting) were [redacted] (55.8%) for hospital setting, [redacted] (16.9%) for hospice setting, and [redacted] (27.3%) for home setting. An overview of terminal care costs is presented in CS Table 80.

Costs for the treatment of AEs were included for grade 3 or 4 AEs that occurred in more than 5% of patients during the neoadjuvant or adjuvant treatment phases in the AEGEAN trial. AE frequencies for the perioperative durvalumab and neoadjuvant PDC arms are derived from AEGEAN. For nivolumab + PDC, surgery alone, and adjuvant PDC, AE frequencies were obtained from publicly available sources. An overview of AE frequencies, costs, and associated sources are presented in Table 4.7 in Section 4.2.7.

EAG comment: The main concerns of the EAG relate to: a) the proportion of patients receiving IO in post recurrence health states, b) the distribution of PDC types in the neoadjuvant setting, c) the exclusion of wastage costs, and d) the assumptions used to inform TDT for the neoadjuvant nivolumab + PDC arm.

a) Subsequent treatment distributions in the post recurrence (i.e., LRR and DM) health states of the company's base-case depend on whether a patient has received IO in the EF health state, and on IO retreatment restrictions. For patients that received IO as a neoadjuvant or adjuvant therapy in the resectable setting, eligibility for post-recurrence retreatment with IO in the CS is granted if they have not progressed within 6 months of completing previous IO treatment. For all patients eligible for post-recurrence IO treatment, 70% and 80% of patients are assumed to receive IO in the LRR and DM1 health states. The EAG questions the validity of i) the 6 month cut-off utilised, and ii) the percentage of eligible patients that received IO:
    i. The use of a 6-month cut-off to determine patient eligibility for IO retreatment post recurrence was justified in response to CQ B18 with reference to TA823 and TA876, and validation by UK clinical experts in an Advisory Board, who suggested that 6 months should be the primary analysis. As per the clinical expert consulted by the EAG, 6 months corresponds to the minimum cut-off for which NHS England will reimburse IO retreatment. In response to CQ B18, the company provided a scenario also based on clinical expert input from the same Advisory Board, utilising an alternative cut-off time point of 1 year. The scenario reduced the deterministic base-case ICER for perioperative durvalumab to £4,011 and £4,365 versus neoadjuvant PDC and adjuvant PDC, respectively. The ICER increased to £23,261 versus neoadjuvant nivolumab + PDC and remained dominant versus surgery alone. Provided the uncertainty surrounding the most reliable cut-off point, the EAG utilised 6-month in its base-case and explored the alternative cut-off time point of 1 year in a scenario analysis.

ii. For LRR, 70% of patients deemed eligible for IO received subsequent IO (i.e., CRT followed by durvalumab) treatment based on the proportion of patients assumed to receive non-BSC treatment in TA798. For DM1, 80% was assumed based on patients assumed to receive non-BSC in TA683 and TA770. Patients were deemed eligible if they received IO treatment in the EF health state and did not progress within 6 months, or did not receive IO in EF, and had PD-L1 ≤1% (informed by AEGEAN). It remains unclear to the EAG whether the utilised distributions are reflective of clinical practice in England and Wales. To assess the impact of the utilised proportion of eligible patients assumed to receive IO treatment in the LRR and DM1 health states, and in the absence of evidence-supported alternative values, the EAG varied the proportion of patients from 70% and 80% to 50% for both LRR and DM1.

b) Neoadjuvant PDC type distributions were informed by AEGEAN mITT data for the perioperative durvalumab + PDC and neoadjuvant PDC arms. The EAG requested justification as to the reflectiveness of these distributions for clinical practice in England and Wales. The company highlighted that, based on insights from a UK Advisory Board, clinical experts confirmed that carboplatin is relevant in resectable NSCLC as a platinum agent for platinum-based chemotherapy, and that it may be seen more frequently than cisplatin in UK clinical practice. Whilst the EAG recognise that a higher share of patients received carboplatin-based PDC (73% and 74% for perioperative durvalumab and neoadjuvant PDC arms, respectively), relative to cisplatin-based PDC (27% and 26% for perioperative durvalumab and neoadjuvant PDC arms, respectively), it notes that the expert input does not justify the plausibility of the specific distributions utilised. However, the Advisory Board summary report provided by the company suggests the AEGEAN trial was considered applicable to patients in the UK by advisors. Two advisors in the report further suggest that they do not use cisplatin and only use carboplatin as a platinum agent. This raises questions regarding the distributions utilised for PDC in the neoadjuvant nivolumab + PDC arm which utilises a higher share of patients receiving cisplatin-based PDC than carboplatin-based PDC in both the neoadjuvant and adjuvant setting. PDC distributions were informed by CheckMate 816 in the neoadjuvant setting and TA876 in the adjuvant setting for the neoadjuvant nivolumab + PDC arm. The company recognise that the EAG had concerns regarding distributions in TA876 but, in the absence of alternative data to inform PDC, considered the approach to be conservative. However, the reasons for which are unclear to the EAG. The clinical expert consulted by the EAG found the utilised distributions to be reasonable in the neoadjuvant nivolumab + PDC arm. As such, the EAG conducted no further analyses with regards to PDC type distribution.

c) Perfect vial sharing was assumed (i.e., no wastage costs) in the CS base-case for IV chemotherapy. In response to CQ B23, the company provided a scenario including wastage costs. The scenario analyses resulted in ICERs of £4,681, £19,776, dominant, and £4,126 versus neoadjuvant PDC, neoadjuvant nivolumab + PDC, surgery alone, and adjuvant PDC, respectively. The company considered the approach to be in line with NHS practice, given hospitals are expected to optimise treatments administered on the same day. However, provided the relatively small size of the population (1,860 in England and Wales estimated to have stage IIA-IIIB resectable, treatment-naïve NSCLC), the EAG considers the assumption to be unrealistic and, in the absence of a plausible estimate for the proportion of vial-sharing, the EAG adopts the company's scenario (i.e., no vial-sharing) in its base-case. When implementing this analysis into its base-case, the EAG noted that the treatment acquisition costs including

wastage for nintedanib were set to 0. As nintedanib is orally administered, the EAG equated this cost to the value excluding wastage.

d) To inform acquisition costs, TDT for neoadjuvant nivolumab in the neoadjuvant nivolumab + PDC arm was estimated using durvalumab TDT from AEGEAN. This was justified in response to CQ B19 as a simplifying approach, assuming that durvalumab TDT would represent TDT for IO treatments. Further, PDC TDT in the neoadjuvant nivolumab + PDC arm was informed by the AEGEAN perioperative placebo arm, assuming that neoadjuvant PDC TDT in the placebo arm would provide a more accurate representation of TDT for non-IO treatments. The EAG recognises the difficulty in sourcing TDT for neoadjuvant nivolumab (TA876 did not explicitly consider treatment discontinuation, assuming all patients would incur the full cost of a treatment course). The EAG consulted clinical expert further considered the approach to be reasonable. As such, the EAG accepts the approach taken by the company.

4.2.10 Severity

A severity Section was not provided in the initial CS. Upon request, the company provided absolute and proportional QALY shortfall stating that the Hernandez Alava et al. QALY shortfall calculator was used. The EAG utilised the QALY Shortfall Calculator by Schneider et al.[60] using the reference case (MVH value set + HSE 2014 ALDVMM model, Hernandez Alava et al.[49]) to replicate the results presented in CQ response Table 45.

The following features were used to inform QALY shortfall calculations for neoadjuvant PDC and neoadjuvant nivolumab + PDC comparators:

- Age of the patient population: 64 (AEGEAN)
- % female in the patient population: 28% (AEGEAN)
- Remaining (discounted) QALYs of the untreated for neoadjuvant PDC: 5.90
- Remaining (discounted) QALYs of the untreated for neoadjuvant nivolumab + PDC: 6.93

Table 4.13 contains the QALY shortfall analysis results, as replicated by the EAG.

Table 4.13: QALY shortfall analysis results

Comparator	Expected total QALYs		QALY shortfall	
	General population	People living with the condition with current treatment	Absolute shortfall	Proportional shortfall
Neoadjuvant PDC	11.24	5.90	5.34	47.53%
Neoadjuvant nivolumab + PDC	11.24	6.93	4.31	38.37%
Based on CQ response Table 45[5] CQ = clarification question; PDC = platinum-doublet chemotherapy; QALY = quality-adjusted life year				

EAG comment: The EAG were able to reproduce the results provided by the company. The EAG would prefer to also see QALY shortfall analyses for the surgery alone and adjuvant PDC comparator arms, as it remains unclear why the QALY shortfall calculation was only provided for two comparators.

4.2.11 Uncertainty

An uncertainty Section was not provided in the original CS. Upon request, the company provided considerations for uncertainty in response to CQ B31. The company highlighted uncertainty for assessing perioperative durvalumab due to the absence of long-term EFS and OS data beyond the trial's follow-up period. The company also consider this uncertainty to have been addressed through the use of various methods to extrapolate EFS beyond the trial duration.

EAG comment: The EAG agrees that the lack of long-term EFS and OS is a great source of uncertainty in the current submission.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

The CS base-case cost effectiveness results (probabilistic), as updated following clarification response, indicated that perioperative durvalumab is both more effective (incremental QALYs of [redacted], [redacted], and [redacted]) and more costly (incremental costs of [redacted],, [redacted], and [redacted],) than neoadjuvant PDC, neoadjuvant nivolumab + PDC, and adjuvant PDC, resulting in respective pairwise ICERs of £4,709, £19,897, and £4,345 per QALY gained (Table 5.1). Further, perioperative durvalumab is both more effective (incremental QALYs of [redacted])and less expensive (incremental costs of [redacted],) than surgery alone, consequently resulting in surgery alone being dominated. The net health benefit (NHB) was calculated for both £20,000 and £30,000 willingness-to-pay (WTP) thresholds. Probabilistic NHB (£20,000 WTP threshold [£30,000 WTP threshold]) for perioperative durvalumab was 1.14 (1.31), -0.13 (0.13), 2.69 (2.65), and 1.24 (1.41) for neoadjuvant PDC, neoadjuvant nivolumab + PDC, surgery alone, and adjuvant PDC, respectively. At a WTP of £30,000/QALY, the probability of perioperative durvalumab being cost effective versus neoadjuvant nivolumab + PDC is [redacted]. An overview of all model changes made following clarification is provided in Table 5.1.

The EAG calculated the results of a fully incremental analyses using results from the updated company probabilistic base-case. Results are presented in Table 5.2.

Table 5.1: Cost effectiveness results including PAS (updated following clarification responses)

Technology	Total			Incremental (versus durvalumab)			ICER (£/QALY)	iNHB at £20,000	iNHB at £30,000
	Costs	LYs	QALYs	Costs	LYs	QALYs			
Deterministic									
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,709	1.34	1.47
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,897	0.00	0.25
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	2.88	2.81
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,345	1.42	1.55
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

Based on clarification Appendix[10] Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10

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

Table 5.2: Fully incremental probabilistic ICERs

Technology	Total			Incremental			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ICER = incremental cost-effectiveness ratio; LY = life years; QALY = quality-adjusted life year

Overall, the technology is modelled to affect QALYs by:

- Increased EF health state occupancy for perioperative durvalumab + PDC. This resulted in a large pre-progression benefit, in terms of QALYs accrued, for perioperative durvalumab in the EF health state ([redacted]) compared to comparator QALYs accrued in the EF health state (ranging from [redacted] for surgery alone to [redacted] for neoadjuvant nivolumab + PDC).
- Increase OS for perioperative durvalumab + PDC, compared to comparators. The proportion of patients alive was higher for perioperative durvalumab + PDC at year 1 ([redacted]), year 2 ([redacted]), year 5 ([redacted]), year 10 ([redacted]), year 15 ([redacted]), year 20 ([redacted]), and year 30 ([redacted]), compared to all other comparators (CS Appendix J).

Overall, the technology is modelled to affect costs by:

- Higher treatment acquisition costs for perioperative durvalumab + PDC compared with comparators (difference ranging from [redacted] to [redacted]).
- Higher health state costs (HCRU and treatment monitoring) for comparators in post recurrence health states compared with perioperative durvalumab + PDC. Differences ranged from [redacted] to [redacted] for LRR, [redacted] to [redacted] for DM1, and [redacted] to [redacted] for DM2.
- Higher treatment costs (administration costs and treatment acquisition costs) for comparators in post recurrence health states compared with perioperative durvalumab + PDC. Differences ranged from [redacted] to [redacted] for LRR, [redacted] to [redacted] for DM1, and [redacted] to [redacted] for DM2.

An overview of changes implemented in the cost effectiveness model following clarification was provided by the company.

Table 5.3 gives an overview of the implemented changes and the linked EAG comments or clarification response, where applicable.

Table 5.3: Cost effectiveness model changes following clarification

Topic	Change	EAG comment/ clarification response
Proportion of patients receiving RT versus CRT in LRR across all comparator arms	RT from 82%-> 18% CRT from 18%->82%	CQ B5 response
Frequency of neutropenia in the durvalumab arm	From 8.7% to 9.0%	Section 4.2.7 Adverse Events, EAG comment a)
Inclusion of additional AEs after decreasing the AE grade 3+ inclusion criteria threshold from 5% to 1%	The following AEs have been added: leukopenia white blood cell count decreased platelet count decreased thrombocytopenia vomiting asthenia decreased appetite	Section 4.2.7 Adverse Events, EAG comment a)

Topic	Change	EAG comment/ clarification response
The CHOOSE formula in the number of AEs for the selected comparator was incorrect due to a typo	Correcting the CHOOSE formula: =CHOOSE(selected_comparator_full_list,E47, E48,,E49) where the second comma was leading to no AEs being attributed to the selected comparator when that was adjuvant PDC in the model	Section 4.2.7 Adverse Events, EAG comment d)
The calculation of QALY loss divides the time duration of AEs by the number of days in a week rather than days in a cycle, causing the duration to be over calculated	Change the formula from: SUMPRODUCT(p_AEsFreq.Durvalumab,p_disutility,p_AE.Duration.Durvalumab/days_per_week) to SUMPRODUCT(p_AEsFreq.Durvalumab,p_disutility,p_AE.Duration.Durvalumab/days_per_month)	Section 4.2.7 Adverse Events, EAG comment d)

AE = adverse event; CQ = clarification question; CRT = chemoradiotherapy; EAG = External Assessment Group; LRR = locoregional recurrence; QALY = quality-adjusted life year; RT = radiotherapy

EAG comment: The main concerns of the EAG relate to: a) the observed versus extrapolated results for total costs and QALYs, and b) incorrectly displayed results for a fully incremental analysis.

a) Median EFS follow-up in censored patients was 11.7 months. When comparing total costs and QALYs in the observed period (rounded to 12 months) and in the extrapolated period (subsequent 35 years) in the economic model, the majority of incremental gains are found in the extrapolated period. That is, the proportion of incremental QALYs found in the extrapolated period accounted for [redacted] of total incremental QALYs for perioperative durvalumab versus comparators across the whole time horizon. Further, incremental costs for perioperative durvalumab in the extrapolated period were negative versus comparator arms (ranging from [redacted] to [redacted]) and positive in the observed period (ranging from [redacted] to [redacted]). Provided the concerns expressed by the EAG associated with the extrapolation of relative effectiveness and costs, the EAG questions the plausibility of the net benefit accrued post-observation.
b) In the clarification response, Table 46, the company provided probabilistic results for a fully incremental analysis. The EAG noted that the treatment strategies were not in an ascending order in terms of total costs or QALYs. Further, the updated cost effectiveness model provided by the company in its clarification response provides alternative probabilistic results to a fully incremental analysis. Here, interventions are ordered in ascending order of total costs, however the results are incorrectly displayed with all incremental costs, incremental QALYs and ICERs presented showing a pairwise comparison with the durvalumab arm. The EAG recalculated probabilistic results for a fully incremental analyses, results for which are presented in Table 5.2.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses. A PSA was performed with 1,000

iterations with results including total costs, life years gained (LYG), QALY, incremental cost per QALY and NHB for perioperative durvalumab versus each comparator (CS Tables 90, 92, and 93).

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

Consistently, modelling assumptions that relate to these parameters likely have the greatest effect on the ICER. This is illustrated by the following CS scenarios that have a substantial impact on the ICER (in at least one of the comparisons):

- EFS HR: applied to standard extrapolations
- EFS distribution for neoadjuvant PDC arm: Weibull
- EFS distribution for neoadjuvant PDC arm: loglogistic
- Discounting costs/effects: 1.5%
- Mean EF utility from Andreas et al. 2018
- No IO retreatment permitted

EAG comment: The main concerns of the EAG relate to: a) the exclusion of relevant input parameters from the DOWSA, and b) the exclusion of probabilistic scenario analyses results.

a) Many relevant input parameters (e.g. treatment shares and distribution parameters to LRR and DM when patients experience an event) were excluded from DOWSA and PSA. The EAG requested an updated economic model with the DOWSA conducted including all input parameters, with the exception of fixed unit prices and general population mortality. The company suggested that an updated DOWSA was conducted including all parameters included in the PSA. This suggestion does not align with the updated economic model provided by the company. Many relevant input parameters are excluded from both the PSA and DOWSA in updated model. The EAG would like to see an updated PSA and DOWSA including all parameters, with the exception of unit prices and general population mortality.
b) All scenario analyses provided in response to CQs were only provided deterministically. In response to CQ B34, the company justified this due to the time required for running probabilistic scenario analyses for all model comparators. The EAG recognise the time-consuming nature of running all scenario analyses probabilistically in the economic model. However, the EAG would prefer that all scenario analyses are provided probabilistically in addition to the deterministic results provided.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

Clinical validation was conducted in an Advisory Board with six UK clinical experts. No detail regarding specific validation or results was provided.

5.3.2 Technical verification

According to the CS, a health economist formally validated the cost effectiveness analysis for internal accuracy. No detail regarding the specific checks or results was provided. Further, a Health Economics

and Outcomes Research (HEOR) consultancy internally validated the model. Similarly, specific detail regarding check and results of the validation were not provided.

In response to CQ B29, the company combined results of the model validation conducted by the model developer and a third-party HEOR consultancy, which encompassed four distinct phases, into a single section. The following phases were included in the validation with results displayed in clarification response Tables 37-44:

- Model inputs (bottom-up): cell-by-cell verification of user editable model parameters and all settings screen parameters
- TECH-VER checklist
- Comments on the overall model architecture
- Additional quality checks, including: validating the use of best evidence, cross-validating against published evidence, parameter and replication-based checks, and assessing the Macro/VBA in the model

5.3.3 Comparisons with other TAs

In the CS, Table 29 and Appendix G provides an overview of model types, comparators used, and EAG considerations for identified TAs. No clear comparison regarding input parameters and estimated outcomes per comparator/intervention with other TAs was provided in CS Section B.3.12 or Appendix G.

5.3.4 Comparison with external data used to develop the economic model

No clear comparison with external data used to develop the economic model was provided in CS Section B.3.12.

5.3.5 Comparison with external data not used to develop the economic model

No clear comparison with external data not used to develop the economic model was provided in CS Section B.3.12.

EAG comment: The main concerns of the EAG relate to: a) Health Economic Advisory Board summary report not provided, b) requested model outcome validity assessments not provided, c) the transparency of expert opinion to inform the model, d) requested model input validity assessments not provided, and e) the handling of model validation outcomes.

a) A summary report was provided for the AEGEAN Health Economic Advisory Board held on 19 January 2024. The document highlights that the document has not been reviewed by the participating clinical advisors and that a full meeting report is to be finalised and shared with clinical advisors for review and comment. The EAG wishes to see the finalised report, approved by the participating clinical advisors.
b) In CQ B27, the EAG requested that model outcome validity was assessed through comparisons to: evidence used to develop the economic model, and evidence not used to develop the economic model. The company state that modelled effectiveness was validated using data from the NSCLC MACG meta-analysis during the UK Advisory Board, and clinical expert opinion. The response does not provide the comparisons requested. To assess the external validity, the

EAG would like to see the requested comparisons of model outcomes to external data used, and not used, to develop the economic model.

c) In addition to expert opinion from the UK Advisory Board meeting held by the company, expert opinion was also relied upon from previous NICE TAs. In response to CQ B26, the company stated that the following previous NICE TAs were utilised in the CS: TA569, TA531, TA584, TA612, TA632, TA642, TA683, TA684, TA770, TA798, TA705, TA823, TA851, TA876, and TA761. It is unclear to the EAG where expert opinion from the referenced TAs are utilised to inform/validate model inputs. As such, the EAG would like to see a clear overview of how each of the stated previous TAs was used to inform model inputs and assumptions.
d) No comparison was provided for relevant NICE TAs regarding input parameters (related to: clinical effectiveness, HSUVs, resource use and costs) or estimated (disaggregated) outcomes per comparator/intervention (i.e., LYs, QALYs, costs). In response to CQ B28, the company justified no such comparison due to information being, at times, redacted from the public documents. The EAG accepts that no comparisons can be made where information is redacted, however, would prefer to see comparisons for all inputs available. Redacted information can be marked as such for the relevant parameters and outcomes.
e) In response to CQ B29, the company provided the combined results of their model validation exercises. These are presented in clarification response Tables 37-44. The company stated that all issues identified have been addressed in the economic model. It is unclear to the EAG whether the issues identified were present in the original model submitted in the CS. No overview of the changes made was provided in CQ CEM changes document submitted by the company. The EAG would like a detailed overview regarding the model fixes that were implemented, including: the original input, details of the issue and how this has been resolved.

6. Evidence review group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[61]

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al. 2016):[62]

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results + the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case. The 'fixing error' adjustments were combined and the other EAG analyses were performed also incorporating these 'fixing error' adjustments given the EAG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. FEs in the implementation of AE disutility (Section 4.2.8)
   AE utility decrement was divided by the number of model cycles per year

6.1.1.2 Fixing violations

None

6.1.1.3 Matters of judgement

2. No cure assumption (Section 4.2.2)
   Given the uncertainty regarding the plausibility of the (implementation of the) cure assumption and lacking supporting empirical evidence, the EAG considers both the company's cure assumption as well as no cure assumption as potentially plausible alternatives.
3. EF utility capped at age and sex adjusted general population utility (Section 4.2.8)
   The EAG questions the face validity of a higher EF utility value than the general population in a diseased population in the company's base-case and hence capped the EF utility in the EAG base-case to the age-adjusted UK general population norms.
4. Inclusion of wastage costs (no vial sharing) (Section 4.2.9)
   No wastage costs were assumed in the CS base-case for IV chemotherapy. The EAG considers the assumption to be unrealistic and, in the absence of a plausible estimate for the proportion of vial-sharing, the EAG adopts the company's scenario (i.e., no vial-sharing) in its base-case.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

1. No BSC in LRR health state (Section 4.2.2)
   The EAG questions the company's assumption that patients receiving BSC in the LRR health state cannot transit to the DM health state. To explore the impact of this assumption, no BSC in LRR is assumed.
2. Treatment waning: 5-year time horizon (Section 4.2.6)
   The plausibility of a constant EFS HR is uncertain, hence the impact of treatment effect waning was explored adopting a 5-year time horizon.
3. Assume lower proportions of patients that receive IO if IO is permitted in the LRR and DM1 health states as no compelling justification is provided for the CS base-case proportions (Section 4.2.6 and 4.2.9).
   The proportions of patients receiving IO if IO is permitted in the LRR and DM1 health states are both set to 50%.
4. Assuming a 0.2 utility decrement from EF to LRR in line with clinical advice from TA876. The EAG also adjusted the DM1 and DM2 utilities to maintain the increment from LRR to DM1 and LRR to DM2 (Section 4.2.8).
   The EAG considers the utility decrement ([redacted]) from EF to LRR to be relatively small and noted that the EAGs clinical expert in TA876 estimated this utility difference to be 0.15-0.20. [redacted], which the EAG considers questionable.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case
Cure assumption	4.2.2	Unavailability	Analyses requested in CQ B7	+	Explored
Assumption that patients receiving BSC in the LRR health state cannot transit to the DM health state	4.2.2	Methods	Analyses requested in CQ B4	+	Partly explored
State transition modelling approach	4.2.2	Methods	Analyses requested in CQ B6	+/-	No
Estimation and assumptions regarding the EFS HRs	4.2.6	Methods and unavailability	Analyses requested in CQs A24 and B9	+	Partly explored
Estimation of transitions from the EFS health state	4.2.6	Methods	Analyses requested in CQ B10	+/-	No
Relative effectiveness of IO retreatment	4.2.6	Methods and unavailability	Analyses requested in CQ B14	+	No
The estimation of the EF utility	4.2.8	Methods, bias & indirectness and unavailability	Adjust HSUV in scenario analyses	+, +/-	Explored
Proportion of patients receiving IO treatment post-recurrence	4.2.9	Unavailability	Scenario analyses with alternative assumptions regarding proportion of patients receiving IO treatment post-recurrence	+	Explored
Advisory Board summary report	5.3.1	Transparency	Provide further information	+/-	No
Model validation	5.3.2	Methods	Provide further information	+/-	No

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator;
BSC = best supportive care; CQ = clarification questions; DM = distant metastases; EAG = External Assessment Group; EF = event free; EFS = event-free survival; HRs = hazard ratios; HSUVs = health state utility values; ICER = incremental cost-effectiveness ratio; IO = immune-oncology; LRR = locoregional recurrence

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the "EAG sheet" provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic/probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
CS deterministic base-case (updated following clarification responses)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,897	0.00	0.25
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Fixing error (1-Implementation of AE disutility: remove "/cycles_per_year" from calculation)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,908	0.00	0.25
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Matter of judgement (2-No cure applied)							
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	£2,311	0.06	0.06
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£663	1.06	1.08
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,275	-0.23	0.09
Matter of judgement (3-EF utility capped at age and sex adjusted general population utility)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£20,183	-0.01	0.24
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Matter of judgement (4-Inclusion of wastage costs, i.e. no vial sharing)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£19,786	0.01	0.25
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Deterministic EAG base-case 1 (Cure applied)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£20,060	0.00	0.24
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Deterministic EAG base-case 2 (No cure applied)							
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£705	1.05	1.06
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,522	-0.24	0.09
Probabilistic EAG base-case 1 (Cure applied)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,177	-0.13	0.13
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Probabilistic EAG base-case 2 (No cure applied)							
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	£12,786	0.03	0.05
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£1,218	0.97	0.99
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£30,694	-0.35	-0.02

AE = adverse event; CS = company submission; EAG = External Assessment Group; EF = event free; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; PDC = platinum-doublet chemotherapy; QALY = quality-adjusted life year; WTP = willingness-to-pay

Table 6.3: Deterministic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Deterministic EAG base-case 1 (Cure applied)							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£20,060	0.00	0.24
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Deterministic EAG base-case 2 (No cure applied)							
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£705	1.05	1.06
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,522	-0.24	0.09
Scenario Analysis (5 – No BSC in LRR): Cure applied							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£18,659	0.05	0.26
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Scenario Analysis (5 – No BSC in LRR): No cure applied							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£25,479	-0.19	0.10
Scenario Analysis (6 – Treatment waning): Cure applied							
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£62,180	-0.66	-0.33
Scenario Analysis (6 – Treatment waning): No cure applied							
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£139,786	-0.80	-0.49
Scenario Analysis (7 – Alternative IO % in LRR and DM1): Cure applied							
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£890	1.03	1.04
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,819	-0.14	0.15
Scenario Analysis (7 – Alternative IO % in LRR and DM1): No cure applied							
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	£56	0.06	0.06
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£7,318	0.73	0.87
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£30,138	-0.39	0.00
Scenario Analysis (8 – 0.2 decrement to EFS utility for LRR utility): Cure applied							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£18,506	0.06	0.30
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Scenario Analysis (8 – 0.2 decrement to EFS utility for LRR utility): No cure applied							
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	£636	1.16	1.17
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£24,355	-0.17	0.15
Scenario Analysis (9 – 12 month cut-off for IO retreatment): Cure applied							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,467	-0.13	0.16
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	iNHB (£20,000 WTP threshold)	iNHB (£30,000 WTP threshold)
Scenario Analysis (9 – 12 month cut-off for IO retreatment): No cure applied							
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-	-
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	£29,567	-0.37	0.01

BSC = best supportive care; DM = distant metastases; EAG = External Assessment Group; EFS = event free survival; ICER = incremental cost-effectiveness ratio; iNHB = incremental net health benefit; IO = immuno-oncology; PDC = platinum-doublet chemotherapy; LRR = locoregional recurrence; QALY = quality-adjusted life year; WTP = willingness-to-pay

6.3 EAG's preferred assumptions

The estimated EAG base-case ICERs (probabilistic) versus neoadjuvant nivolumab and PDC, based on the EAG preferred assumptions highlighted in Section 6.1, were £24,177 (cure applied base-case) and £30,694 (no cure applied base-case) per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of 45% and 55% (cure applied base-case), and 35% and 48% (no cure applied base-case) at WTP thresholds of £20,000 and £30,000 per QALY gained respectively. The most influential adjustment was applying no cure. The ICER increased most in the scenario analysis with alternative assumptions regarding treatment waning. Moreover, alternative assumptions regarding IO (re)treatment post-progression can also have a substantial upward impact on the ICER.

6.4 Conclusions of the cost effectiveness section

The CS and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data on patients with stage I–III NSCLC who are candidates for, or have previously undergone, surgical resection of the primary NSCLC.[3, 5, 10] Searches were conducted in October 2023 and updated on 11 September 2023 and 14 November 2023. Searches were transparent and reproducible, and comprehensive strategies were used. A broad range of databases, HTA organisation websites and grey literature resources were searched. Overall, the EAG has no major concerns about the literature searches conducted for the costs SLR.

The company's cost effectiveness model mostly complied with the NICE reference case; it was only unclear whether the UK tariff is used for all health state utilities. The most prominent issues highlighted by the EAG were: 1) appropriateness of model structure assumptions, specifically related to cure and the transition between LRR and DM; 2) the use of a state-transition model; 3) the population considered in the analyses; 4) not considering neoadjuvant CRT as comparator; 5) the estimation of EFS and associated HRs; 6) the relative effectiveness of IO retreatment and the proportion of patients receiving IO (re)treatment post-recurrence; 7) the EF utility used and; 8) lacking information related to the company's Advisory Board meeting and model validation.

Firstly, the CS base-case assumes that 95% of patients would achieve cure if they had not experienced an EFS event at 5 years. Moreover, the total proportion of patients assumed to be cured (i.e. 95% of patients remaining in the EF health state at 5 years) was [redacted] for patients that received perioperative durvalumab, neoadjuvant PDC, neoadjuvant nivolumab + PDC, adjuvant PDC and surgery alone respectively. Based on the information available to the EAG, it was unclear whether these proportions as well as the assumption that cure involves maintaining an event-free status for patients until death is plausible. Moreover, the company assumed that patients receiving BSC in the LRR health state cannot transit to the DM health state. This was inconsistent with clinical expert opinion obtained by the EAG. Secondly, the state transition model adopted by the company might be considered a source of methodological uncertainty. It is unclear whether the additional complexity of the state transition model approach is justified, particularly given that the time-dependent transition probabilities for TP4-6 might bias the results. Thirdly, the company did not consider subgroups in the cost effectiveness analyses that were listed in the NICE Final Scope, and it is unclear whether the AEGEAN trial population is representative of the target population in UK clinical practice due to lacking data on the UK target population. The latter can potentially be problematic given there may be important effect modifiers. Fourthly, the company excluded nCRT as a comparator in the economic model. The EAG's clinical expert agrees with the company that nCRT is not a valid comparator, as these patients form a smaller subgroup compared to the ITT population in the AEGEAN trial and treatment modalities are

different. Whilst the EAG accepts that nCRT may not be routinely administered, this does not automatically imply that nCRT is inferior to perioperative durvalumab or eligible for exclusion. Fifthly, the estimation of transitions from the EFS health state and related HRs are uncertain because of methods adopted to estimate the HRs, the time dependency of the HRs and both the time and treatment dependency of the probability of the event being LRR or DM. Sixthly, it is uncertain whether the relative effectiveness of initial IO treatment and IO retreatment in the economic model would be similar (as implicitly assumed by the model) or whether the relative effectiveness of IO retreatment would be diminished compared with initial IO treatment. Seventhly, the EF utility in the company's base-case (based on the AEGEAN trial) was higher than the age-adjusted UK general population utility. This might potentially be due to missing data, and/or given that data from the adjuvant period were not used. Finally, information was lacking regarding the company's Advisory Board meeting and model validation, which makes it challenging for the EAG to assess the credibility of the model results.

The associated uncertainty related to points 1, 2, 3, 4, 5 and 6 are insufficiently explored by the company to assess the potential implications for the estimated cost effectiveness. Hence it would be informative if the company would provide the analyses requested in the clarification letter (independently of the company's judgement on the relevance of these analyses), including CQs A7, A24, B3, B4, B7, B9, B10 and B14.

The estimated EAG base-case ICERs (probabilistic) versus neoadjuvant nivolumab and PDC, based on the EAG preferred assumptions highlighted in Section 6.1, were £24,177 (cure applied base-case) and £30,694 (no cure applied base-case) per QALY gained. The probabilistic EAG base-case analyses indicated cost effectiveness probabilities of 45% and 55% (cure applied base-case), and 35% and 48% (no cure applied base-case) at WTP thresholds of £20,000 and £30,000 per QALY gained respectively. The most influential adjustment was applying no cure. The ICER increased most in the scenario analysis with alternative assumptions regarding treatment waning. Moreover, alternative assumptions regarding IO (re)treatment post-progression can also have a substantial upward impact on the ICER.

There is large remaining uncertainty about the effectiveness and relative effectiveness of perioperative durvalumab as well as IO (re)treatment post-progression, which can be at least partly resolved by the company by conducting further analyses. According to the EAG the current approach (both in the CS and EAG base-case) is suboptimal in terms of model assumptions as well as potential bias due to the state transition approach that both could conceivably change the ICER. Moreover, the current assessment does not provide an appropriate estimation of the comparators listed in the scope. Therefore, the EAG believes that the CS nor the EAG report contains an unbiased ICER of perioperative durvalumab compared with all relevant comparators.

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Single Technology Appraisal

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

EAG report – 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 report to ensure there are no factual inaccuracies or errors in the marking of confidential [redacted] corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5:00pm on Friday 26 April 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 Incorrect interpretation of the time at which DFS would be tested in the MTP

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
• Table 1.4: Key issue 3: Omission of results for DFS, p 17 • Section 3.2.5.2 DFS, p 65 The EAG report states "the statistical analysis of DFS would only occur when there were 400 patients with a minimum of 7 months follow-up." In the AEGEAN clinical study report, the MTP describes hierarchical testing in which DFS was to be tested upon a significant EFS result. As per the MTP, the first interim analysis of EFS was planned to occur when data in the modified intent-to-treat (mITT) population were approximately 30% mature (approximately 224 EFS	Change wording in Table 1.4, p 17 to: *The EAG understands that per the rigorous Multiple Testing Procedure, the first interim analysis with a statistical analysis for DFS would occur upon a significant EFS result. As per the MTP, the earliest testing of DFS would occur after the first interim analysis of EFS that was planned to occur when data in the modified intent-to-treat (mITT) population were approximately 30% mature (approximately 224 EFS events).* Change the wording in Section 3.2.5.2, p 65 to: *In relation to the response above, the EAG understands that, per the rigorous MTP, the first interim analysis with a statistical analysis for DFS would occur upon a significant EFS result. As per the MTP, the earliest testing of DFS would occur after the first interim analysis of EFS that was planned to occur when data in the modified intent-*	To ensure accuracy in the EAG report regarding the correct MTP procedure.	Not a factual inaccuracy. In both instances, the EAG report discusses how DFS, an outcome stipulated in the NICE final scope, could have been analysed.

events). This would be the earliest time DFS statistical testing would occur in AEGEAN.	*to-treat (mITT) population were approximately 30% mature (approximately 224 EFS events).*		

Issue 2 Estimates for the relative and absolute risk for and AE of "death possibly related to any study treatment" presented by the EAG that were not part of the formal statistical analysis plan for AEGEAN

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
• Section 1.6, p 27 • Section 3.2.6, p 83 • Section 3.6, p 113 The EAG report includes estimates for the relative- and absolute risk of "deaths possibly related to any study treatment" for perioperative durvalumab versus perioperative placebo. The AEGEAN statistical analysis plan did not include formal statistical testing for adverse event (AE) results. The published protocol states "Safety data will not be formally analysed but	We request the EAG report includes a note immediately after each mention of relative- and absolute risk estimates for "deaths possibly related to any study treatment" for perioperative durvalumab versus perioperative placebo that states: *The relative- and absolute risk estimates provided by the EAG were not formally tested in AEGEAN and any consideration of these results should be done with due caution*.	There is considerable uncertainty associated with estimates provided that have not been adequately powered for statistical testing.	Amended the three Sections. "It should be noted that the AEGEAN statistical analysis plan did not include formal statistical testing for AE results."

summarised using the safety analysis set, according to the treatment received. Therefore, the relative- and absolute risk estimates provided by the EAG cannot be considered formal AEGEAN results and any consideration of these result should be done with due caution.			

Issue 3 Clarification of the population wording

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
• Section 2.1, p 38 The EAG report states "The company decision problem restricts this population to those with stage IIA to IIIB NSCLC. This appears to be due to the anticipated	We request this sentence be changed to reflect the full wording of the population considered in the submission to say: *The company decision problem restricts this population to those with stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements. This appears to be*	To ensure accuracy of the EAG report regarding the population considered in the submission.	Text in Section 2.1 has been amended to align with text in column "Decision problem addressed in the CS" of Table 2.1.

regulatory licence and regulatory trial." We would like to clarify that the population considered in our submission was "Adults with untreated, resectable, stage IIA to IIIB NSCLC and no known EGFR mutation or ALK rearrangements."	*due to the anticipated regulatory licence and regulatory trial.*		

Issue 4 The EAG report may overstate the efficacy of neoadjuvant chemoradiotherapy in the population relevant to this submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
• Section 2.3, p 39 The EAG's comments on the exclusion of neoadjuvant chemoradiotherapy (nCRT) states: "it should be noted that some references were found that suggest that nCRT may actually have some degree of efficacy in the scope	We request the EAG remove the following sentence from the EAG report due to a lack of strong evidence to support the claim: *Furthermore, it should be noted that some references were found that suggest that nCRT may actually have some degree of efficacy in the scope population.*[6-8]	To ensure accuracy of the EAG report as this sentence is not adequately supported with robust data in published literature and may overstate the efficacy of nCRT in the population relevant to this submission.	Not a factual inaccuracy.

population.[EAG report references 6-8]". Upon looking at these references we would like to highlight that the conclusions of two of these studies do not provide strong evidence of efficacy: The conclusion of reference 6 (Pless et al 2015) states "Radiotherapy did not add any benefit to induction chemotherapy followed by surgery. We suggest that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 non-small-cell lung cancer." The conclusion of reference 7 (Katakami et al 2012) states "The addition of radiotherapy to the induction chemotherapy regimen for stage IIIA (N2) NSCLC appears to confer better local control without adding significant adverse			

events. The favorable local control in this CRS arm did not translate to a significant survival difference. We consider this was due to the small sample size. Tumor down-staging after induction therapy is an important factor for improving patient survival."			

Issue 5 The statement that the omission of the comparator nCRT from the decision problem is based upon clinical opinion and not objective data is not accurate

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
• Section 1.1, p 12 • Section 1.3, p 15, Table 1.2 • Section 2.3, p 39 The EAG report states "The omission of nCRT is made solely because of clinical opinion in the company	We request the EAG report change to say: *The company considered the NICE Final Scope reference to nCRT*	This states the company made a decision to exclude a comparator from the NICE scope based solely on clinical opinion that is factually incorrect.	Not a factual inaccuracy. However, text has been amended to improve clarity.

submission (CS), and further rationale is required." This statement is not correct. The exclusion of nCRT was based on recently published literature that confirmed nCRT was used in a very small proportion of patients in the UK *(Duan et al 2020 reports the population of patients eligible for neoadjuvant CRT is only about 7% of NSCLC patients and Adizie et al, 2019 reported CRT being administered in only 5% of stage IIIA NSCLC patients in England)*, meaning the actual number of patients relevant to the submission was negligible. This was also supported with reference to TA876, where the submitting company provided evidence and maintained that CRT should not be considered as a key comparator for resectable			

NSCLC. Finally, this was further supported by UK clinical expert opinion. On the basis that the number of patients that are treated with nCRT in this patient population in the UK is negligible, it is appropriate to exclude nCRT as a comparator.			

Issue 6 The statement that the NICE Final Scope reference to atezolizumab as a comparator was ignored is not accurate

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
• Section 2.3, p 39 The EAG report states that "The company has ignored the NICE Final Scope reference to atezolizumab as a comparator for the sub-group expressing PD-L1 with at least a 50% tumour proportion score. However, this correctly follows NICE methods guidance that states that "Technologies that NICE has	We request the EAG report change to say: *The company considered the NICE Final Scope reference to atezolizumab and excluded it as a comparator for the sub-group expressing PD-L1 with at least a 50% tumour proportion score. This correctly follows NICE methods guidance that states that "Technologies that NICE has recommended with managed access are not considered established practice*	This states the company ignored the NICE request to include atezolizumab as a comparator that is factually incorrect.	Wording changed in Table 2.1 as well as in Section 2.3.

recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators." We disagree that the NICE Final Scope reference to atezolizumab was ignored. The company submission gives due consideration to atezolizumab as a comparator in Section B.1.1 Decision Problem and Section B.1.3.3 Clinical Pathway of Care. Both sections explain the rationale behind the decision to exclude atezolizumab as a comparator due to it being in managed access ie, atezolizumab was not considered a relevant comparator for the full population or any subgroup as it is not currently approved for routine commissioning. This is aligned with NICE methods	*in the NHS and are not considered suitable comparators."*		

and the EAG agree this approach is appropriate.			

Issue 7 Wording of the definition of DFS

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.2.5.2, p 65 The EAG report states "Disease-free survival is defined as "the time from resection until local or distant disease recurrence in the subpopulation of patients who were disease-free following resection, or death due to any cause, whichever occurs first." The definition of DFS in the published protocol defines DFS as "Disease-free survival is defined as the time from the date of surgery until the first date of disease recurrence (local or distant), or date of death	We request the wording in the EAG report is changed to align with the definition of DFS in the published protocol: *Disease-free survival is defined as the time from the date of surgery until the first date of disease recurrence (local or distant), or date of death due to any cause, whichever occurs first.*	To ensure accuracy in the EAG report	Not a factual inaccuracy. Wording is based on CS e.g., footer of Table 4.

due to any cause, whichever occurs first.”			

Issue 8 The rationale suggested by the EAG for why a formal statistical analysis of OS was not presented in the submission is not accurate

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 3.2.5.5, p 69 The EAG states that the company rationale for not providing a formal analysis of OS was that “i) a longer period is required to collect OS data, and ii) that the measurement of OS may be “confounded by the effects of subsequent therapies used in later lines following recurrence or progression.” These two reasons were presented in our submission as general limitations of using OS as an endpoint in early-stage NSCLC clinical trials. The reason OS was not subject to a formal	We request that the EAG report be changes as follows: *The CS defines OS as the time from randomisation to death. The CS reports that OS was not subject to a formal analysis at the interim cut-off date (10 November 2022); however, the trial is ongoing and OS will be tested at a later planned analysis. In general, there are limitations to using OS as an endpoint in early-stage NSCLC trials that include i) a longer period is required to collect OS data, and ii) that the measurement of OS may be “confounded by the effects of subsequent therapies used in later*	To ensure accuracy of the EAG report in the interpretation of the correct MTP procedures of AEGEAN in relation to the evaluation of OS.	Not a factual inaccuracy. The next two bullet points in the EAG comment in Section 3.2.5.5 stipulate the company response to the request for clarification and a statement that “the lack of a formal analysis of OS was consistent with the pre-hoc MTP plan”.

analysis was that it was part of a MTP in an ongoing trial and will be tested at a later planned analysis.	*lines following recurrence or progression ".*		

Issue 9 The sources referenced in the CS to justify the inclusion of cure are not entirely presented by the EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.2, p 120 The EAG states that the CS relied on consistencies with TA569 and TA642 to justify the inclusion of cure: "In the CS this assumption was stated to be consistent with TA569 (early-stage breast cancer) and TA642 (relapsed or refractory acute myeloid leukaemia)." However, this is not entirely accurate since several sources beyond these were utilised. This included Sonoda et al. 2019 (used in TA823), TA876 and TA761.	We request that the EAG report be changes as follows: *"In the CS this assumption was stated to be consistent with TA569 (early-stage breast cancer) and TA642 (relapsed or refractory acute myeloid leukaemia), TA823 (resected non-small-cell lung cancer), TA876 (resectable non-small-cell lung cancer) and TA761 (resected non-small-cell lung cancer)."*	To ensure accuracy of the EAG report in line with the CS.N	Not a factual inaccuracy. This sentence in the EAG report was based on CS Table 30 "Characteristics of de novo economic model". Here the assumption of cure was supported by (only) referring to TA569 and TA642

Issue 10 Extrapolation approaches used for transitions from the DM health state are not reported correctly

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.3, p 129 The EAG states that "In cases where a piecewise approach was utilised, the curves with the best statistical fits, as determined by AIC/BIC, were selected (CS Appendix M)." This is an inaccuracy since piecewise models were not utilised to inform transitions from the DM health state (only standard parametric models). If a piecewise model was utilised in the base case from a referenced TA, then the same parametric distribution that had the lowest AIC/BIC was applied	We request that the EAG report be changes as follows: *"In cases where a piecewise approach was utilised, the curves with the best statistical fits, as determined by AIC/BIC, were selected and applied to a standard parametric model (CS Appendix M).*	To ensure accuracy of the EAG report in line with the CS.	Not a factual inaccuracy. This sentence (without the reference to CS Appendix M) was directly copied from CS Section B.3.3.5.

to the entire duration to avoid complexity.			

Issue 11 Distribution of treatments in the LRR health state for radiotherapy (RT)

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 4.2.6.4, p 130 In Table 4.6, the proportion of patients receiving RT in the LRR health state including IO (re)treatment is noted as 34.8%, and not including IO (re)treatment is 65.2%. The proportion of patients receiving RT + cisplatin + etoposide was reported as 7.6% (including IO (re)treatment) and 14.3% (not including IO (re)treatment). The Source/assumption column states that 82% receives RT and 18% receives CRT.	The percentages in the table should be changed as follows: RT: 7.6% (including IO (re)treatment) and 14.3% (not including IO (re)treatment). RT + cisplatin + etoposide: 34.8% (including IO (re)treatment) and 65.2% (not including IO (re)treatment). The Source/assumption column should state: *"Consistent with TA761 (based on UK clinical expert opinion), it was assumed that (of those patients that do not receive IO or BSC), 18% RT and 82% CRT."*	A reporting error picked up in the EAG clarification questions was not updated in the reported table.	Not a factual inaccuracy. The EAG report section highlighted is a summary of the original CS. The change/correction is described in Table 5.3 of the EAG report.

These numbers were updated after the ERG clarification questions after an error in the reporting was identified.			

Issue 12 Typographical errors in the EAG report

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Section 1.6 p 29 ICERs in Table 1.22 presenting: 1) EAG_3 Matter of judgement results 2) EAG base-case 1 (cure applied) probabilistic results are not reported correctly (taking LYs instead of QALYs into account in the calculation of £/QALY)	Table has been reconstructed to fix the reported ICERs and to increase clarity of the results. In addition, we have updated all fully incremental analysis results provided in the final EAG report. The updated tables shown in **addendum 1** compare all comparators directly to the intervention (perioperative durvalumab), rather than to the comparator with the lowest total cost.	The updated tables in addendum 1 ensure a comprehensive evaluation of each comparators cost-effectiveness relative to perioperative durvalumab and aligns with the typical pairwise ICER reporting in NICE submissions. Therefore, these tables should replace the format utilised in the EAG report.	Not a factual inaccuracy. The EAG does not consider tables presented in addendum 1 to be fully incremental analyses (as highlighted, for instance, by Paulden 2020, https://doi.org/10.1007/s40273-020-00914-6 section 2.2). As such, addendum 1 tables have not been adopted.

Section 3.1.5, p 50 The database searches returned 5,925 (and 6,576 in the October 2023 update) unique articles from database searches.	5,925 needs to change to 5,927 in this sentence		Amended accordingly.
Section 3.2.5.4.3, p 69 Table 3.12 has a missing footnote.	Please add this note to the bottom the table: [a] Includes patients with missing baseline scans or missing pre-surgery scans		Amended accordingly.
Section 3.2.5.7.1, p 74 "Being sex or smoking status appeared to make an appreciable difference to the point estimate."	Rewording the start of this sentence may help with readability and accuracy.		Amended accordingly.
Section 3.2.6, p 79 Table 3.17 needs a superscript b added to the Decreased appetite cell Table 3.20 needs an additional header row	Table 3.17 change: *Decreased appetite*[b] Table 3.20 change: Add *Discontinuation category (Overall Period*[a]*)* in column 1, and		Table 3.17: Amended accordingly. Table 3.20: Not a factual inaccuracy. Based on Table 28 of the CS.

	Number (%) of patients[b] as a merged cell across columns 2 and 3.		
Section 3.3.1, p 84 Spelling error in the trial name	Change the spelling of AUGEAN to AEGEAN		Amended accordingly.
Section 3.3.2, p 84 ”To evaluate perioperative durvalumab to the remaining two comparators in the decision problem (neoadjuvant PDC , and active monitoring) an NMA was set up, rather than conducting two pairwise MAICs.”	This sentence should refer to adjuvant PDC and active monitoring as the comparators for the NMA rather than neoadjuvant PDC and active monitoring.		Amended accordingly.
Section 6.2, p 159 (Table 6.2 and Table 6.3)	Tables have been reconstructed to fix the reported ICERs and to increase clarity of the results		Tables 1.22 and 6.2: Amended accordingly. Table 6.3: Not changed as it does not display results for EAG_3 or for EAG probabilistic base-case 1 (cure applied).

ICERs in Table 6.2 and Table 6.3 presenting: 1) EAG_3 Matter of judgement results 2) EAG base-case 1 (cure applied) probabilistic results are not reported correctly (taking LYs instead of QALYs into account in the calculation of £/QALY)			

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG comment**
Section 1.4, Table	Wording related to interpr	For the OS outcome, which yielded a result suggesting the two arms were [redacted] on the 10 November 2022 DCO point, data from the safety-analysis cut-off point at 120 days were also presented.	Amended accordingly.

1.5, p17	etation of the OS outcome should be marked as CIC		
Section 1.6, p 27	Wording related to interpretation of the HRQoL outcome should be marked as CIC	HRQoL [redacted] between intervention and comparator.	Amended accordingly.
Section	Wording	The CS[3] then reports results from the safety analysis cut-off date at 120 days ([redacted]).	Amended

3.2.5, p 71	related to the date of the safety analysis cut-off data should be marked as CIC		accordingly.
Section 3.2.5, p 71	Wording related to the hazard ratio outcomes should be marked as CIC	This showed a HR of [redacted] (95% CI [redacted] to [redacted].	Amended accordingly.

Section 3.4.2, p 101	Wording related to the NMA outcomes from the CS should be marked as CIC	"[redacted] *and as a result of excluding Rosell 1994 and Li 2009, statistical heterogeneity (I2) was reduced from* [redacted] *in the base case analysis to* [redacted] *in sensitivity analysis 2.*	Text is marked as CiC.
Section 4.2.9.2.4, Table 4.11, p 141	EF health state (informed by "Tx Shares & Costs" worksheet), Neoadjuvant PDC	£[redacted]	Amended accordingly.

	Treatment costs per cycle – should be marked as CIC		

Addendum 1

We have updated all fully incremental analysis results provided in the final EAG report. The updated tables shown below compare all comparators directly to the intervention (perioperative durvalumab), rather than to the comparator with the lowest total cost. This ensures a comprehensive evaluation of each comparators cost-effectiveness relative to perioperative durvalumab and aligns with the typical presentation format in NICE submissions. Therefore, these tables should replace the format utilised in the EAG report.

EAG comment: See responses related to EAG report tables 1.22, 6.2, and 6.3 above.
The EAG does not consider tables presented in addendum 1 to be fully incremental analyses (as highlighted, for instance, by Paulden 2020, https://doi.org/10.1007/s40273-020-00914-6 section 2.2). As such, this is not a factual inaccuracy and the addendum 1 tables have not been adopted.

Table 1. CS deterministic base-case (updated following clarification responses)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,897	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,709	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,345	[redacted]	[redacted]

Table 2. Fixing error (1-Implementation of AE disutility: remove "/cycles_per_year" from calculation)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,908	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,708	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,344	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Durva dominant	[redacted]	[redacted]

Table 3. Matter of judgement (2-No cure applied)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,275	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,995	[redacted]	[redacted]

Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,706	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,968	[redacted]	[redacted]

Table 4. Matter of judgement (3-EF utility capped at age and sex adjusted general population utility)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,183	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,776	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,406	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Durva dominant	[redacted]	[redacted]

Table 5. Matter of judgement (4-Inclusion of wastage costs, i.e. no vial sharing)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-

Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,786	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,680	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,125	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Durva dominant	[redacted]	[redacted]

Table 6. Deterministic EAG base case 1 (cure assumption)

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,060	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,747	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,184	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Durva Dominant	[redacted]	[redacted]

Table 7. Deterministic EAG base case 2 (no cure assumption)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,522	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,124	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,647	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,040	[redacted]	[redacted]

Table 8. Probabilistic EAG base case 1 (cure assumption)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,177	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,181	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,871	[redacted]	[redacted]

Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Durva dominant	[redacted]	[redacted]

Table 9. Probabilistic EAG base case 2 (no cure assumption)

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,694	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,628	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,635	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Durva dominant	[redacted]	[redacted]

Table 10. Scenario Analysis (5 – No BSC in LRR): Cure applied

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,659	[redacted]	[redacted]

Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,447	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£1,962	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£4,130	[redacted]	[redacted]

Table 11. Scenario Analysis (5 – No BSC in LRR): No cure applied

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,479	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,209	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,812	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,870	[redacted]	[redacted]

Table 12. Scenario Analysis (6 – Treatment waning): Cure applied

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-

Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£139,780	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,180	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,477	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,375	[redacted]	[redacted]

Table 13. Scenario Analysis (6 – Treatment waning): No cure applied

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£139,786	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£62,183	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,480	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,376	[redacted]	[redacted]

Table 14. Scenario Analysis (7 – Alternative IO % in LRR and DM1): Cure applied

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**

Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,819	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,321	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,697	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,575	[redacted]	[redacted]

Table 15. Scenario Analysis (7 – Alternative IO % in LRR and DM1): No cure applied

Technologies	**Total costs (£)**	**Total LYs**	**Total QALYs**	**Incremental costs (£) [Durva vs.]**	**Incremental LYs [Durva vs.]**	**Incremental QALYs [Durva vs.]**	**ICER (£) [Durva vs.]**	**Incremental NHB (£20,000) [Durva vs.]**	**Incremental NHB (£30,000) [Durva vs.]**
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,138	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,415	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,881	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,049	[redacted]	[redacted]

Table 16. Scenario Analysis (8 – 0.2 decrement to EFS utility for LRR utility): Cure applied

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,506	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,334	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,822	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£1,491	[redacted]	[redacted]

Table 17. Scenario Analysis (8 – 0.2 decrement to EFS utility for LRR utility): No cure applied

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,355	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,115	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,686	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,605	[redacted]	[redacted]

Table 18. Scenario Analysis (9 – 12 month cut-off for IO retreatment): Cure applied

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,467	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,397	[redacted]	[redacted]
Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,844	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£1,868	[redacted]	[redacted]

Table 19. Scenario Analysis (9 – 12 month cut-off for IO retreatment): No cure applied

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) [Durva vs.]	Incremental LYs [Durva vs.]	Incremental QALYs [Durva vs.]	ICER (£) [Durva vs.]	Incremental NHB (£20,000) [Durva vs.]	Incremental NHB (£30,000) [Durva vs.]
Perioperative durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Neoadjuvant nivolumab + PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,567	[redacted]	[redacted]
Neoadjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,814	[redacted]	[redacted]

Adjuvant PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,346	[redacted]	[redacted]
Surgery alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,821	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with non-small-cell lung cancer or caring for a patient with non-small-cell lung cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

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Patient expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with non-small-cell lung cancer

Table 1 About you, non-small-cell lung cancer, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with non-small-cell lung cancer ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with non-small-cell lung cancer ? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): Husband of wife who died of non-small-cell lung cancer in 2019
3. Name of your nominating organisation	National Institute for Health and Care Excellence (NICE)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with non-small-cell lung cancer? **If you are a carer (for someone with non-small-cell lung cancer) please share your experience of caring for them**	My wife [redacted] was diagnosed with stage 4 non-small-cell lung cancer in early 2017 though she had been ill with increasingly high levels of back pain and persistent chest infections from around September 2016, around the time I had major heart surgery myself. [redacted] was registered disabled from corrective surgery to remove multiple tumours in her spine so mobility was a huge issue for her. As the disease advanced, the tumours metastasised to her brain and bones. But her main issue from the beginning was depression and anxiety which kicked in almost immediately after diagnosis. She increasingly suffered from crying, agoraphobia, anxiety, loss of hope and inability to engage with the people who loved her. Our son also has a chronic health condition; unfortunately he was only 15 when she was diagnosed, and the impact of her suffering on him was, and still is, enormous. The diagnostic process was traumatic and is a useful background: I took her to our local casualty on a Saturday in January 2017 unable to walk, sit or lie without severe pain but even though we eventually found out her back was broken in several places we were discharged and told to arrange an appointment with her GP on the Monday. I refused to accept that and took her then to another hospital who admitted her straight away. After a week or so, they diagnosed spinal secondaries and she was transferred to a world renowned spinal unit in a different hospital, where a team of surgeons rebuilt her spine. She was discharged home- now disabled - after two and a half months in hospital. I believe our appalling experience in that A&E department had a detrimental and long lasting impact on her mental health and quality of life, which indirectly affected what she got out of her treatments. We experienced both the best and the worst of the NHS on that long and difficult journey. She died in a hospice on Friday September 13, 2019 spending two and half months there.

	Though I was working full-time, I was able to do that from home so I could attend to [redacted]'s needs. That included a wide variety of things such as lifting objects she couldn't pick up, helping her walk, washing, shopping, cooking, cleaning, taking our son to school, ordering and giving her medication, driving her to multiple appointments, advocating for her in and out of hospital, handling her state benefits, trying to help her psychologically, being in constant touch with our GP; traveling to the hospital or hospice when she was an impatient, loading her pill tray; the list goes on. She was unable to walk upstairs to the bathroom, so with the help of a crowdfunding campaign I organised, we raised enough money to build a garden room with a shower, sink and toilet which was helpful. Overall, caring for her was shattering and all-consuming, especially while trying also to look after our son. I suffered from the physical manifestations of anxiety - including dizziness, visual disturbance, eczema - as a result of what we were going through. Needless to say it was difficult to fulfil my obligations at work, but thankfully, my employers were incredibly understanding. In summary, [redacted]'s overall quality of life was adversely affected by her difficulty in walking, severe pain in her back, constipation caused by morphine tablets, difficulty caring for herself, anxiety and depression and her dependence on me for many of her everyday needs.
7a. What do you think of the current treatments and care available for non-small-cell lung cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	I am only am only aware of the treatments [redacted] received and they are, in my view, a two-edged sword. On diagnosis, she was given a few months to live, but after spinal surgery and the targeted therapies of first gefitinib and then osimertinib, she lived for 2 years and 8 months after diagnosis; far longer than her doctors expected. The gefitinib shrank her tumours, but stopped being effective after 18 months. The osimertinib was effective for perhaps 8 months. As there is so little hope for people diagnosed with later stage NSCLC, the fact that there are drug treatments at all is incredibly important. I remember the elation we felt when we discovered that [redacted] was genetically compatible with the therapies she was given. However, these treatments should in my view be given alongside advocacy,

	counselling and psychological support, as well as honest and detailed information about management of side-effects and drug efficacy for this incredibly vulnerable group of patients. In my view, the terminally ill are the most vulnerable group of patients the NHS cares for. Their needs, especially their psychological needs, are so often left unmet. It was clearly positive that [redacted] lived to see our son's sixteenth and seventeenth birthdays, and witnessed him getting into college to study science. Precious moments we will treasure. We managed to go away on holiday twice, though by the second holiday her agoraphobia and diarrhoea were so severe, so never left the cottage.
8. If there are disadvantages for patients of current NHS treatments for non-small-cell lung cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Though the drug therapies extended her life expectancy, her quality of life was increasingly poor, though I suspect this was mostly as a result of her condition, not side-effects from the drugs. However, the side effects were sometimes difficult: severe diarrhoea at times being the worst, but loss of appetite too. Itching and a skin rash affected her but her precarious mental health meant she used the medication as an excuse to avoid sunlight and stay indoors. She seemed, for example, to fixate on various skincare products which she believed were unsafe to use while taking the medication, when there was no evidence of that. I often felt it might cheer her up if she had a small gin as she had enjoyed a 'drink' in happier times, though I was not able to convince her to do that, despite reassurances from her clinicians and I suspect that distorted concerns over the side effects of the drugs were a factor in this. Indeed, I sometimes found it difficult to be able to distinguish between genuine and perceived side-effects because her mental health was so precarious. She received little if no meaningful psychological care which might have made her final few years easier and perhaps derive more benefit from the medication. Both the gefitinib and osimertinib were taken orally and were prescribed after hospital visits, entailing long waits at our hospital pharmacy, though we discovered we could wait for the drugs to be dispensed at a Maggies centre nearby, a wonderfully welcoming place and so unlike anything we'd seen before in the health system. I think very sick and terminally ill patients should be prioritised in pharmacies so they do not have to wait too long, or at least can wait in comfort.

	[redacted] found it easy to swallow the tablets, but was increasingly confused about when and which tablets to take. I seem to remember her taking at least 30 pills day, so explanation and support on taking medication is essential for these patients.
9a. If there are advantages of Durvalumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Durvalumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	As durvalumab will be the first immune-oncology therapy to be used for the perioperative treatment of NSCLC, I think that is a significant and important advantage. It does seem tremendously exciting. In my view, other advantages include: Durvalumab given as IV given during outpatient visits could be an advantage for a number of reasons. As ordering and supervision of the drug is carried out by clinical staff and not the carer, I would think that might ease the pressure on carers- just one thing less to worry about you might say. If a patient has someone who is able to drive them to appointments and accompany them while there, then getting out of the house could also be helpful for patients and carers, even if it is to hospital. [redacted] would otherwise rarely agree to leave the house. As participants taking perioperative durvalumab are 32% less likely to have their cancer come back or die compared to those taking perioperative placebo over a median time of 11.7 months, this is a significant advantage. However, I think stratification between the mortality and returning cancer figures would be helpful information: I couldn't find them in the notes. And the good toleration of perioperative durvalumab was also a significant advantage, especially when compared to what [redacted] went through. In particular, I am impressed that it did not affect people's ability to have four cycles of chemotherapy and did not exacerbate the side-effects related to surgery, or any complications of surgery. I do feel that this drug or any other cancer drug should be

	given alongside good psychological care and counselling for patients to derive the most benefit from them.
10. If there are disadvantages of Durvalumab over current treatments on the NHS please describe these. For example, are there any risks with Durvalumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	It's difficult for me to answer this. This drug seems to be very beneficial and suitable for a range of patients.
11. Are there any groups of patients who might benefit more from Durvalumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I'm not aware of any patients who in my view might benefit more than others. However, I would like to understand why patients with unresectable late stage three and stage four NSCLC are excluded from the treatment group.
12. Are there any potential equality issues that should be taken into account when considering non-small-cell lung cancer and Durvalumab? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	Older people may need more support getting to and around hospital if they are to be given equitable access to the therapy. I managed to convince [redacted] to use a wheelchair, as there was much waiting and standing around at our hospital. Though [redacted] was relatively young- she died aged 52 – I think her mobility and other support needs were comparable to a much older person. Parking was so stressful, as I had to drop her off sat the entrance and then leave her while I searched for a parking spot, rushing back to the hospital so she wasn't alone for too long.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No
14. Do you consider that the utility values for the different health states shown in Table 4.8 reflect your experience with NSCLC? As a point of reference, a utility value of 1 is generally considered to be akin to perfect health. A utility value of 0.829 was estimated to be the average utility for the UK population when matched to the AEGEAN clinical trial for age and sex.	Yes

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- This drug seems to be very beneficial and suitable for some patients in terms of efficacy and side effects.
- High quality psychological support will enhance the beneficial effects of this drug.
- Expected side effects need to be clearly explained to patients along with details on how best to manage them as well as why this drug is only suitable for patients with resectable early stage 3 NSCLC.
- The needs of carers must be taken into account when making decisions
- Multiple hospital visits should be accompanied by well organised parking, good general support and guidance from staff to ensure stress and anxiety for patients and carers is as minimal as possible.

Thank you for your time.

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