in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

Draft guidance consultation – Additional evidence

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1. Additional clinical evidence

1.1 AEGEAN Trial Interim Analysis 2 Results

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

1.1.1 Event free survival

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

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

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

[a] Calculated using the Kaplan-Meier technique.

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

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

1.1.2 Disease free survival

These results were reported for the first time.

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

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

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

[a] Calculated using the Kaplan-Meier technique.

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

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

1.1.3 Overall survival

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

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

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

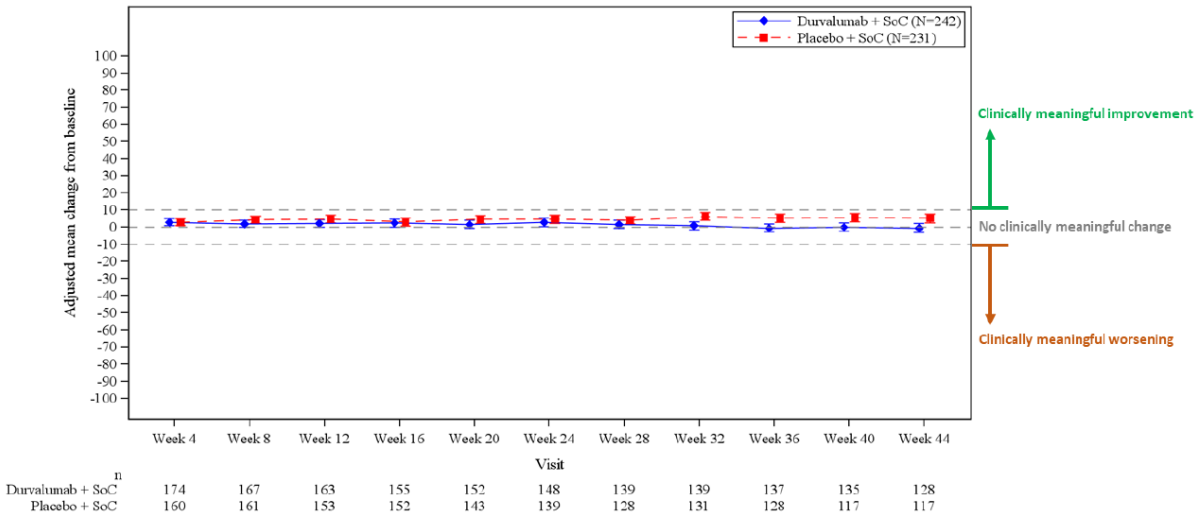
[a] Calculated using the Kaplan-Meier technique.

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

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

1.1.4 Health related quality of life

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



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

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

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

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

1.1.5 Adverse events

Table 1.4: Adverse events

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

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

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

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

1.2 Updated Match-Adjusted Indirect Comparison Results

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

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

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

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

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

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

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

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

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

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

1.3 Updated Network-Meta Analysis Results

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

The methods remained the same.

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

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

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

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

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

1.4 Multilevel Network Meta-Regression Feasibility Assessment

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

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

1.5 Time-Varying Hazards Analysis

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

1.5.1 Results for MAIC versus neoadjuvant nivolumab

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

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

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

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

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

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

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

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

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

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

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

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

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

2. Additional Economic Evidence and Updated Cost-Effectiveness Results

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

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

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

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

Table 2.1: Cost effectiveness results including PAS

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

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

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

2.1.1 Reproducing company's updated base-case

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

2.2 EAG comments

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

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

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

EAG comment: The EAG believes this adjustment is reasonable.

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

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

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

EAG comment: The EAG believes this adjustment is reasonable.

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

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

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

EAG comment: The EAG believes this adjustment is reasonable.

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

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

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

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

Table 2.2: EFS piecewise (3 + months) HRs

	HR (95% CI) versus neoadjuvant PDC	Method
Perioperative durvalumab	[redacted]	MAIC weighting to CheckMate-816
Neoadjuvant nivolumab + PDC	[redacted]	MAIC weighting to CheckMate-816
Surgery alone	[redacted]	Random effects NMA
Adjuvant PDC	[redacted]	Random effects NMA

CI = confidence interval; CS = company submission; EFS = event-free survival; HRs = hazard ratios; PDC = platinum-doublet chemotherapy; MAIC = matching adjusted indirect comparison; NMA = network meta-analysis

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

EAG comment: The EAG believes this adjustment is reasonable.

2.2.5 Company's sensitivity and scenario analyses

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

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

- Starting age of the model should be set to 70 years in line with the likely NHS clinical practice population (ACM 3.7)
    - Scenario 14 - Starting age at 70 years
- Proportional hazards assumption relaxed, and time varying-hazard ratios fully explored. This would allow the uncertainty in the treatment effect estimates, derived from potential changes to the underlying hazards, to be better explored (ACM 3.9).
    - Section 2.4.2.3.1 - Time-varying hazards scenario
- In the absence of clinical data, the company should provide scenarios exploring different time points and proportions assumed to be cured as well as scenarios without a cure assumption (ACM 3.15).
    - Scenario 1 - Apply a warm-up period of 12 months starting from year 5
    - Scenario 2 - Apply cure at 6 years for both arms
    - Scenario 3 - No cure applied

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

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

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

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

2.3 EAG proposed additional analyses

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

> "*The committee acknowledged the evidence, but noted that there was no longer-term evidence supporting the presence or absence of treatment effect waning in the NSCLC perioperative setting. The committee considered that treatment effect waning was only likely to have a substantial effect on the cost effectiveness results of the model if it occurred before the cure point (see section 3.15). It concluded that additional modelling of treatment effect waning would be less important in scenarios that applied a cure assumption and that explored time-varying hazard ratios in the NMA (see section 3.9). But it also noted that in the scenarios that did not apply a cure assumption (see section 3.15), additional treatment effect waning should be explored*" (Section 3.10).

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

> "*The CDF clinical lead explained that because neoadjuvant nivolumab was only recently recommended, numbers accessing retreatment were still very low and it was difficult to provide accurate figures or evidence on retreatment efficacy*" (Section 3.14).
>
> "*The committee concluded that there was limited evidence on the efficacy of immunotherapy retreatment and that this issue was associated with unresolved uncertainty in the modelling*" (Section 3.14).

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

3. References

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

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

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

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