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

Second committee meeting [ACM2]

For ZOOM – contains no CON information

Technology appraisal committee A [10th September 2024]

Chair: James Fotheringham

External assessment group: Kleijnen Systematic Reviews

Technical team: Rachel Williams, Samuel Slayen, Christian Griffiths, Ian Watson

Company: AstraZeneca

ACD: preliminary recommendation

Durvalumab is not recommended, within its marketing authorisation, as neoadjuvant treatment with platinum-based chemotherapy, then alone as adjuvant treatment, for treating NSCLC in adults whose cancer is resectable and has no EGFR mutations or ALK rearrangements

Committee made this decision as it was unable to establish a plausible ICER due to substantial uncertainty around:

- the indirect treatment comparison used and its effects on the EFS hazard-ratio (DG 3.6)
- the appropriateness of the proportional hazards assumption and maintenance of treatment effect beyond the observed data (DG 3.9)
- the appropriateness of a cure assumption and the cure proportion and point modelled (DG 3.15)

Consultation responses received from:
AstraZeneca (company)

Abbreviations: ALK, anaplastic lymphoma kinase; EFS, event-free survival; EGFR, epidermal growth factor receptor; DG, draft guidance; ICER, incremental cost effectiveness ratio; NSCLC, non-small-cell lung cancer

Key issues

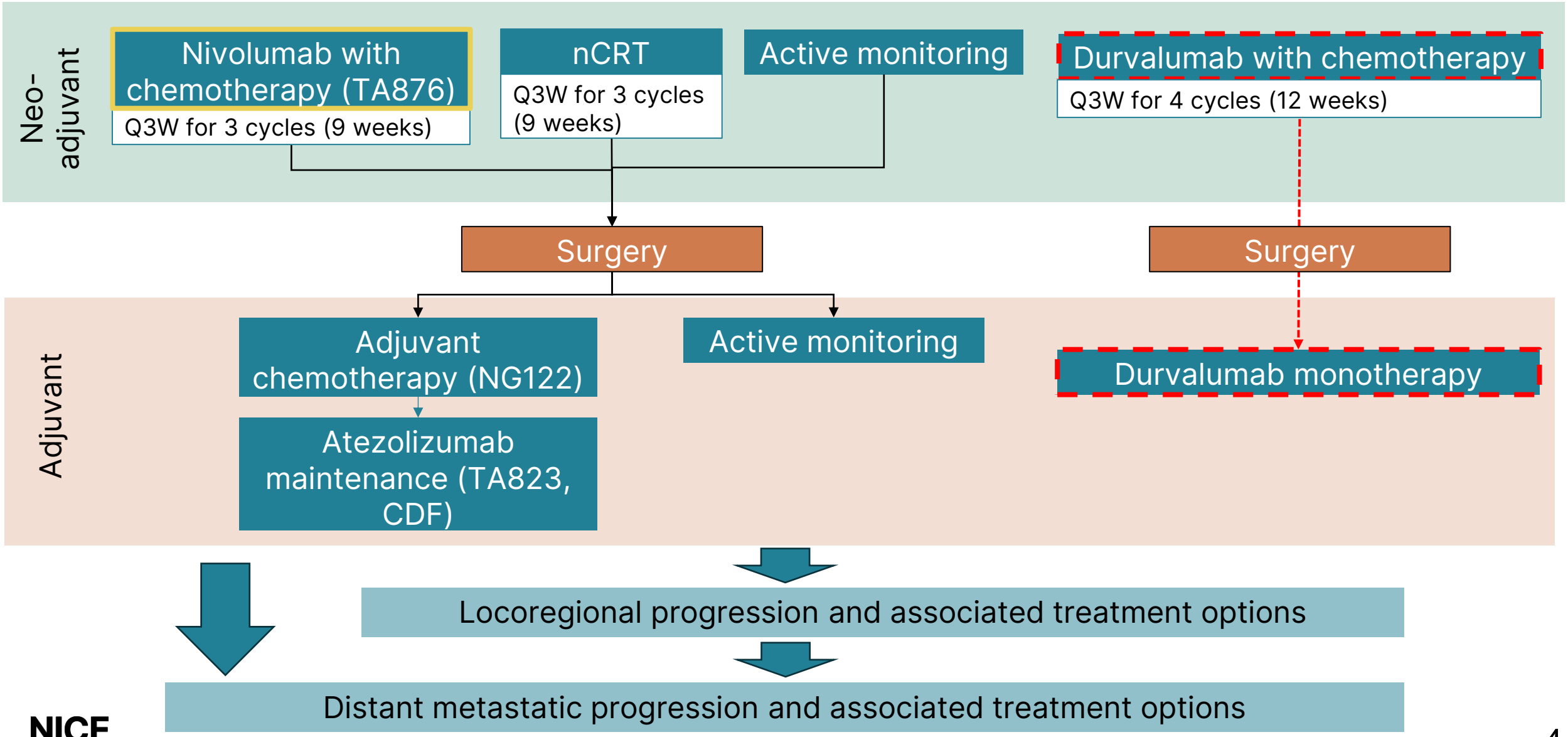
Issue	DG section	New analyses/evidence submitted?	ICER impact versus neoadjuvant nivolumab + PDC
Indirect treatment comparison (ML-NMR)	3.6	No. Feasibility assessment suggested ML-NMR not appropriate.	Unknown
Time-varying HRs	3.9	Yes. Time varying EFS HRs have been explored for the: • MAIC comparing against neoadjuvant nivolumab from the CheckMate-816 study • NMA comparing against adjuvant chemotherapy and surgery alone	Large
Appropriateness of modelling cure assumption	3.15	Yes. Scenarios provided exploring a 6-year cure point, a 12-month cure warm-up period starting from year 5, and a no cure scenario.	Small to moderate

Abbreviations: DG, draft guidance; EFS, event-free survival; ICER, incremental cost effectiveness ratio; MAIC, matching adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NMA, network meta-analysis; PDC, platinum-doublet chemotherapy

Treatment pathway (resectable NSCLC)

RECAP

Committee concluded neoadjuvant nivolumab is most relevant comparator



Abbreviations: CDF, cancer drugs fund; nCRT, neoadjuvant chemoradiotherapy; Q3W, every 3 weeks

Durvalumab (Imfinzi, AstraZeneca)

RECAP

	Durvalumab treatment info
Marketing authorisation	• IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of adults with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangement
Mechanism of action	• Durvalumab is a checkpoint inhibitor targeting and blocking PD-L1 which is responsible for dampening T-lymphocyte immune responses in the tumour microenvironment • It is used with chemotherapy in the neo-adjuvant phase to prime the immune system and slow tumour growth and as a monotherapy in the adjuvant phase to target micro-metastases
Administration	• Neoadjuvant: 1500mg in combination with platinum chemotherapy, Q3W for four cycles • Adjuvant: 1500mg monotherapy Q4W for up to 12 cycles after surgery
Price	• List price is £2466 per 500mg vial • Estimated total cost of a full course of therapy per person is £69,779 • A confidential commercial access agreement applies to durvalumab

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Abbreviations: EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed cell death ligand 1; mg, milligrams; Q4W, every four weeks

Clinical effectiveness

RECAP

AEGEAN trial

- Randomised controlled trial compared perioperative durvalumab with perioperative placebo (neoadjuvant chemotherapy and placebo followed by adjuvant placebo) in resectable NSCLC (stage 2A to 3B N2)
- Primary outcomes: EFS and pathological complete response
- Interim analysis (November 2022) used for the company submission

Indirect treatment comparisons

- MAIC (adjusting for all possible effect modifiers) compared perioperative durvalumab to neoadjuvant nivolumab. A 0-3 month, a 3 month+, and a full MAIC were conducted, with 3 month+ used in base case
- The adjusted sample from AEGEAN was also used to inform the hazard-ratio for neoadjuvant chemotherapy (not a comparator but reference curve in model)
- NMA used to compare to non-IO comparators

ITC methods

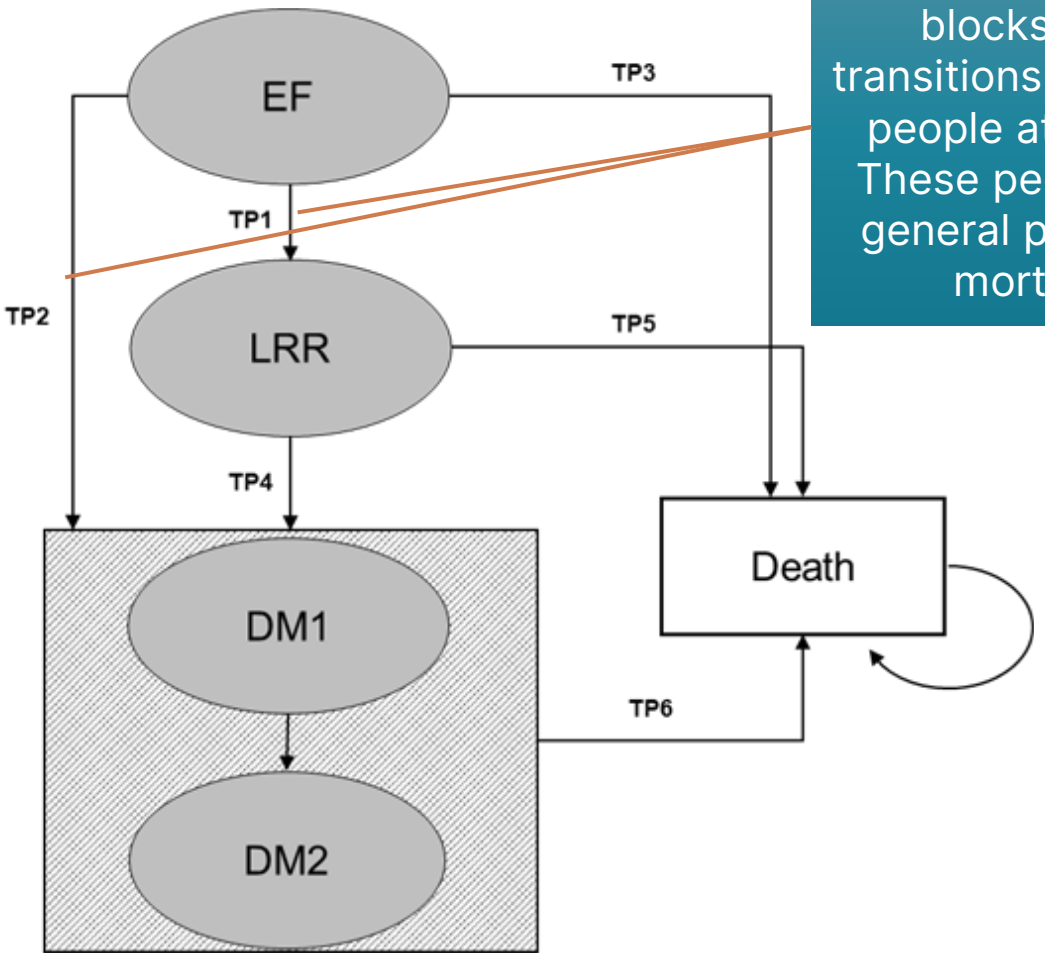
ITC networks

Abbreviations: CI, confidence intervals; EFS, event-free survival; HR, hazard ratio; IO, immuno-oncology; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis; NSCLC, Non-small-cell lung cancer

Company's model overview

RECAP

Model structure



Cure assumption blocks these transitions for 95% of people at 5 years. These people have general population mortality.

- Technology affects **costs** by:
  - Durvalumab incurs higher drug treatment costs
  - Affecting HCRU and subsequent treatment costs in post-recurrence health states
- Technology affects **QALYs** by:
  - Increasing EF state occupancy compared to comparators
  - Increase in overall survival and thus life years gained and QALYs (including cure effect)
- Assumptions with greatest ICER effect:
  - Modelling of cure point and proportion
  - EFS HR versus neoadjuvant chemotherapy
  - Waning of treatment effect
  - Utility in the LRR state

Details of modelling of EFS

NICE

Abbreviations: EF, event-free; LRR, loco-regional recurrence; DM, distant metastases; TP, transition probability; HCRU, health care resource use; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Consultation responses

NICE National Institute for Health and Care Excellence

Consultation response

Comments and additional evidence received from AstraZeneca

Additional and updated evidence includes:

- New data cut (IA2) as detailed in clinical effectiveness section (including disease-free survival)
    - Existing MAIC updated with most recent data
    - Update of transition probabilities 1 to 3 (EF to LRR, DM and death) in the model with new data and ITC results
- Feasibility assessment for ML-NMR
- Exploration of time-varying hazard ratios
- Scenario analyses conducted to assess the impact of cure assumptions

Abbreviations: EF, event-free; DM, distant metastases; HR, hazard ratio; IA, interim analysis; ITC, indirect treatment comparison; LRR, loco-regional recurrence; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; TP, transition probability

Company response overview for key issues at ACM1 (1/3)

Remains a key issue at ACM2

Key Issue (DG section)	Committee conclusion	Company draft guidance response
Indirect treatment comparison and the EFS hazard ratio (3.6)	"… that it would like to see supplementary approaches using ML-NMR explored to compare perioperative durvalumab with neoadjuvant nivolumab adjusted to different target populations" (NHS and AEGEAN)	• Feasibility assessment determined that ML-NMR was inappropriate due to heterogeneity of effect modifiers
Transitions from EF to LRR and DM health states (3.8)	"…changing the proportions did not have a large effect on the cost-effectiveness estimates but concluded that it preferred to model transitions out of EF based on the proportions seen in the AEGEAN trial"	• Company updated base-case to include the NICE committee preferred assumption EAG: adjustment is reasonable
Appropriateness of a proportional hazards assumption and maintenance of treatment effect beyond the observed data (3.9)	". . . wanted to see the proportional hazards assumption relaxed, and time-varying hazard ratios fully explored"	• Exploration of time-varying hazard ratios were conducted in scenario analysis
Treatment effect waning (3.10)	"…in the scenarios that did not apply a cure assumption, additional treatment effect waning should be explored"	• No comment (company's no cure scenario does not explore treatment effect waning)

Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; DM, distant metastases; EFS, event-free survival; LRR, loco-regional recurrence; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression

Company response overview for key issues at ACM1 (2/3)

Remains a key issue at ACM2

Key Issue (DG section)	Committee conclusion	Company draft guidance response
Immunotherapy retreatment (3.14)	"...preferred to model 60% as having retreatment with immunotherapy at subsequent stages"	• Company updated base-case to include the NICE committee preferred assumption EAG: adjustment is reasonable
Appropriateness of modelling cure assumption (3.15)	". . . likely to be appropriate to model a cure assumption in some form, although this was uncertain. . . " ". . . in the absence of clinical data, the company should provide scenarios exploring different time points and proportions as well as scenarios without a cure assumption"	• There is strong precedent for capturing cure and committees in TA761, TA823 and TA876 accepted cure assumptions • Provided scenarios for a 12-month warm-up period starting from year 5, a 6-year cure timepoint, and no cure
Health state utility values (3.16)	"...prefer to use the EAG's decrement scenario for decision making"	• Company updated base-case to include the NICE committee preferred assumption EAG: adjustment is reasonable

Abbreviations: ACM, appraisal committee meeting; DFS, disease-free survival; DG, draft guidance; EFS, event-free survival

Company response overview for key issues at ACM1 (3/3)

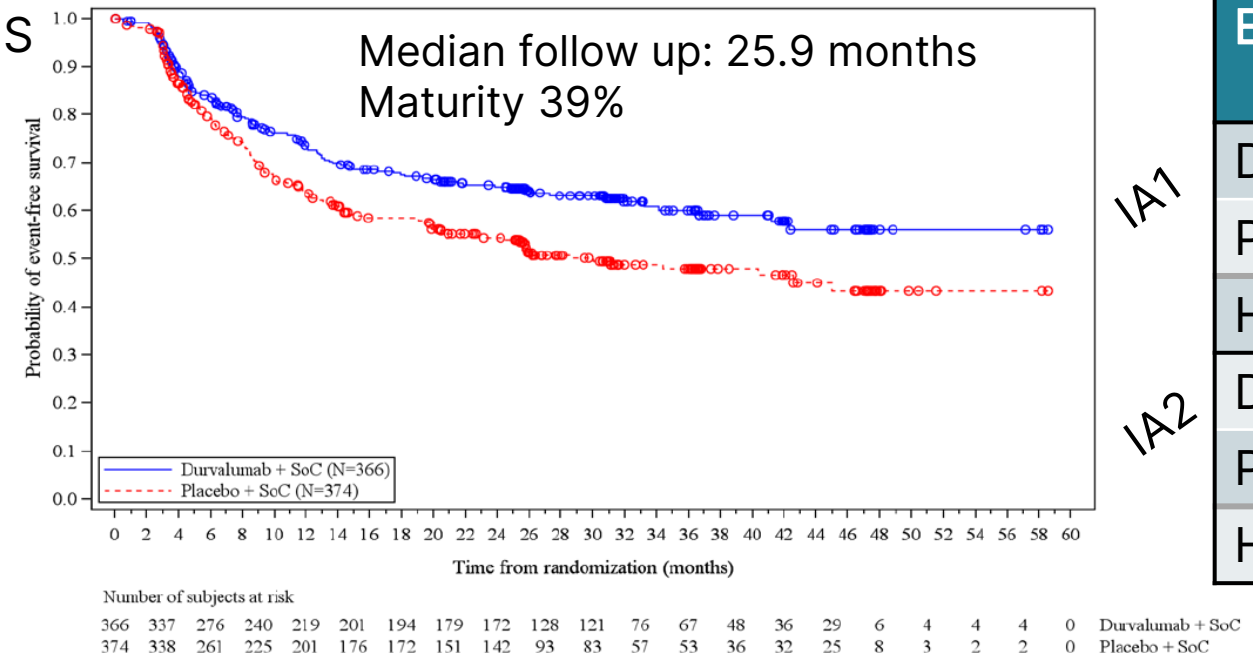
Other issue (DG section)	Committee conclusion	Company draft guidance response
Further data-cuts (3.18)	"…further data from the AEGEAN trial, if available, might help to resolve some of the uncertainty in the modelling"	• Company have provided second interim analysis with updated EFS and OS, and reporting of DFS. EAG: incorporation of updated EFS in model is reasonable
Age of diagnosis (3.4 and 3.7)	". . .there were some key differences between both trials and NHS clinical practice (such as disease stage and age) that would need to be accounted for in the ITC and the modelling" "…concluded that the starting age of the model should be set to 70 years in line with the likely NHS clinical practice population"	• Disagrees with committee's conclusion. Age not an effect modifier, and the 74 years median age from the NLCA does not represent the early stage, resectable population. • Provided a scenario for a 70-year starting age • Considers the proportion of patients in AEGEAN with specific stages is consistent with the NLCA. All potential treatment effect modifiers were adjusted for in the base case, consistent with DSU guidance
Reporting of outcomes (3.5)	". . . other outcomes listed in the scope including DFS, adverse events, and health related quality of life had not been reported"	• Factual inaccuracy. Adverse events and HRQoL were reported. • Presented DFS results available at IA2

Abbreviations: ACM, appraisal committee meeting; DFS, disease-free survival; DG, draft guidance; HRQoL, health-related quality-of-life; ITC, indirect treatment comparison; NLCA, National Lung Cancer Audit

Company response and EAG critique

Updated clinical effectiveness results (AEGEAN) – IA2

EFS



EFS	Events/patients (%)	Median EFS (95%CI)
IA1 Durvalumab	98/366 (26.8)	NR (31.9 to NR)
IA1 Placebo	138/374 (36.9)	25.9 (18.9 to NR)
IA1 HR (95% CI)		0.68 (0.53 to 0.88)
IA2 Durvalumab	124/366 (33.9)	NR (42.3 to NR)
IA2 Placebo	165/374 (44.1)	30.0 (20.6 to NR)
IA2 HR (95% CI)		0.69 (0.55 to 0.88)

	EAG comment
EFS	• Difference between the two DCOs is minimal overall • Survival advantage maintained at 36 months
OS	• Continues to be little difference between the two arms of AEGEAN • Numerical advantage appears to shift towards perioperative durvalumab

OS	Perioperative durvalumab	Perioperative placebo
IA1 Death IA1	81/366 (22.1)	82/374 (21.9)
IA1 HR (95%CI)	1.02 (0.75 to 1.39)	
IA2 Death IA2	121/366 (33.1)	140/374 (37.4)
IA2 HR (95%CI)	0.89 (0.70 to 1.14)	

More IA2 results

NICE

Abbreviations: CI, confidence intervals; DCO, data cut off; EFS, event-free survival; NR, not reached; HR, hazard-ratio; IA, interim analysis; OS, overall survival

Updated ITC results

More MAIC results

- MAIC has been rerun with AEGEAN IA2 results and using CheckMate-816 4-year data cut (3 year used at ACM1)
- Neoadjuvant chemotherapy reference curves of model have been updated with IA2 EFS (TP1 to 3, event-free to LRR, DM and Death)

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]											

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.

Company's ACM2 base case EFS HR

EAG comments

- Results of the MAIC were largely unchanged between EFS IA1 and IA2 analyses

Abbreviations: ACM, appraisal committee meeting; DM, distant metastases; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HR, hazard-ratio; IA, interim analysis; LCL, lower control limit; LRR, loco-regional recurrence; m, months; MAIC, matching-adjusted indirect comparison; PDC, platinum-doublet chemotherapy; TP, transition probability; UCL upper control limit

Key Issue: ITC used to compare to neoadjuvant nivolumab

Background (ACM1)

- Committee: only 1 method of indirect comparison used, adjusted to population that may not reflect NHS practice (CheckMate-816). Requested analyses using ML-NMR adjusted to different target populations

Company

- ML-NMR was considered including all relevant comparators in the network
- Not feasible to conduct a robust ML-NMR:
  - Reliant on shared effect modifier assumption which is not appropriate due to:
    - Heterogeneity of effect modifiers (may bias estimates if assumption not met)
    - Inappropriate to assume same effect modification between perioperative durvalumab and neoadjuvant nivolumab because, in certain subgroups, (1) there were larger differences in EFS HRs in CheckMate-816 than in AEGEAN, and (2) the direction of effect modification was different in each trial
  - Insufficient IPD and aggregate data to estimate treatment effect and independent effect modifier interactions, or to test validity of shared effect modifier assumption with adequate power
- CheckMate-816 considered generalisable to UK clinical practice in TA876 so considered appropriate to match to.

EAG comments

- 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
- But this must be weighed against the limitation of using different methods of evidence synthesis, (1) for the comparison with neoadjuvant nivolumab and (2) for the comparison with all other comparators

Is the ITC evidence suitable for decision making?

Abbreviations: EFS, event-free survival; HR, hazard ratio; IPD, individual patient data; ITC, indirect treatment comparison; ML-NMR, multilevel network meta-regression

Key Issue: Time-varying hazard ratios in the MAIC (1/2)

Background (ACM1)

- Committee wanted to see proportional hazards assumption relaxed, time-varying hazard ratios explored

Company

- Base case time-constant EFS HR for perioperative durvalumab versus neoadjuvant nivolumab + platinum chemotherapy updated to [redacted] (95% CI [redacted]) with data from IA2 (3+ month time interval)
- Conducted time-varying hazards using MAIC with parametric models fitted to weighted data from AEGEAN. Fixed and random effects models fitted but only fixed were used due to very wide CrIs in the random effects model
- Lognormal considered most appropriate and used in base case to extrapolate EFS. EFS hazard ratio [redacted]
- Time-varying hazard ratios [redacted] time-constant hazard ratio for most of the model. Use time-constant hazard ratio in base case as conservative assumption
- Time-varying hazard ratio approach shows the proportional hazards assumption is violated in first few months but holds afterwards, supporting use of the piecewise approach

EAG comments

- Log-normal model appears to be a reasonable choice (see choice of distribution slide)

Abbreviations: ACM, appraisal committee meeting; CI, confidence interval; CrI, credible interval; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; MAIC, matching-adjusted indirect comparison; PH, proportional hazards

Key Issue: Time-varying hazard ratios in the MAIC (2/2)

EFS time-varying and constant hazard ratios (versus nivolumab)

Are time-constant (piecewise) or time-varying EFS HRs preferred for decision making?

Abbreviations: ACM, appraisal committee meeting; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PH, proportional hazards

Key Issue: Cure assumption

Background (ACM1)

- Committee would have preferred to see cure modelled directly from clinical data. In the absence of this, company should explore different time points and proportions as well as a scenario without cure.
- Committee also noted that in scenarios without a cure assumption, treatment effect waning should be explored

Company

- Functional cure concept well established in this area. Strong precedent for capturing cure (TA761, TA823, TA876)
- Provided scenarios looking at:
  - a 12-month warm-up period starting from year 5 (cured proportion increases gradually from 0% to 95%)*
  - a 6-year cure timepoint
  - a conservative assumption where no cure is modelled (without treatment effect waning)
- Retained 95% cured at five years assumption in base case

EAG comments

- EAG continues to present its base case with cure (95% at 5 years, as in the company base case) and without cure (without treatment effect waning) assumption applied

Should cure be modelled and, if so, what are the committee's preferred assumptions?

NICE

Abbreviations: ACM, appraisal committee meeting

*When warm up period is implemented HCRU costs are suspended for entire cure proportion at the start of the warm-up period.

Issue: Model starting age

Background (ACM1)

- Committee considered that the model should use a starting age of 70 years to be in line with the assumed NHS clinical practice population

Company

- Median age of 74 years taken from the NLCA report does not represent the resectable population.
- Disagree that there were key differences in age that need to be accounted for in the modelling
- Retain a base case model starting age of 64 years to reflect the AEGEAN trial
- Explored a starting age of 70-years in scenario analysis

EAG comments

- No comments

What model starting age should be used for decision making?

Abbreviations: ACM, appraisal committee meeting; NLCA, National Lung Cancer Audit

Summary of company and EAG base case assumptions

Assumptions matching committee base case in company and EAG base case

Parameter	Assumptions from ACM1 DG used in company ACM2 base case
Proportion of EF events LRR or DM	Used AEGEAN proportions ([redacted]) for all interventions.
EFS utility value	EFS utility capped at general population with EAG utility decrement scenario
Eligibility for subsequent IO	Proportion of eligible patients having IO at LRR and DM set to 60%

Other assumptions

Parameter	Committee base case at ACM1	Company ACM2 base case	EAG base case
Cure assumption	Some form of cure appropriate, requested scenario exploration.	Retains 95% cured at 5 years (Provides 12-month warm-up, no cure, and 6-year cure scenarios)	One base case with cure as per company base case One base case with cure removed
Model starting age	70 years to reflect broad midpoint between AEGEAN and NLCA all cases median age	Retains 64 years as starting age	64 years

Abbreviations: ACM, appraisal committee meeting; AE, adverse events; DG, draft guidance; DM, distant metastases; EFS, event free survival; IO, immuno-oncology treatment; LRR, locoregional recurrence; NLCA, National Lung Cancer Audit

Summary of additional scenarios

Key scenarios presented by the company in response to draft guidance consultation

Parameter	Base case	Scenario
Cure-point warm up period	No warm-up period. 95% cured at 5 years	1 year warm up (roughly linear increase from 0% at 5 years to 95% at 6 years)
Later cure-point	95% cured at 5 years	95% cured at 6 years
No cure applied	95% cured at 5 years	No cure
EFS HR	Piecewise time-constant (log-normal)	Time-varying HR
Starting age	64 years	70 years

EAG comments:

- Draft guidance consultation indicated:
  - additional treatment effect waning should be explored in scenarios without a cure assumption
  - uncertainty related to the relative effectiveness of immunotherapy retreatment
- Scenarios exploring these parameters might be informative

Abbreviations: EFS, event-free survival; HR, hazard ratio

Cost-effectiveness results

Cost effectiveness results cannot be reported here due to presence of confidential discounts for included technologies

The company and EAG base case ICERs versus neoadjuvant nivolumab + PDC are below £30,000 per QALY gained

All results are presented in Part 2 slides for committee consideration

Abbreviations: ICER, incremental cost effectiveness ratio; PDC, platinum-doublet chemotherapy; QALY, quality adjusted life-year

Backup slides

NICE National Institute for Health and Care Excellence

NMA/ITC methodology

MAIC and NMA to compare perioperative durvalumab with comparators

- Anchored MAIC compared perioperative durvalumab to neoadjuvant nivolumab with chemotherapy
- MAIC had a base case (all possible effect modifiers) and scenario (only weighting on characteristics imbalanced between trials). Base case MAIC used to inform base case of the model.
- NMA compared perioperative durvalumab to surgery alone, neoadjuvant chemotherapy and adjuvant chemotherapy
- Company preferred random effect models over fixed effect models.
- NMA had a base case and four sensitivity analyses which excluded studies for various reasons. Sensitivity analysis 2* was used in the base case for the model.

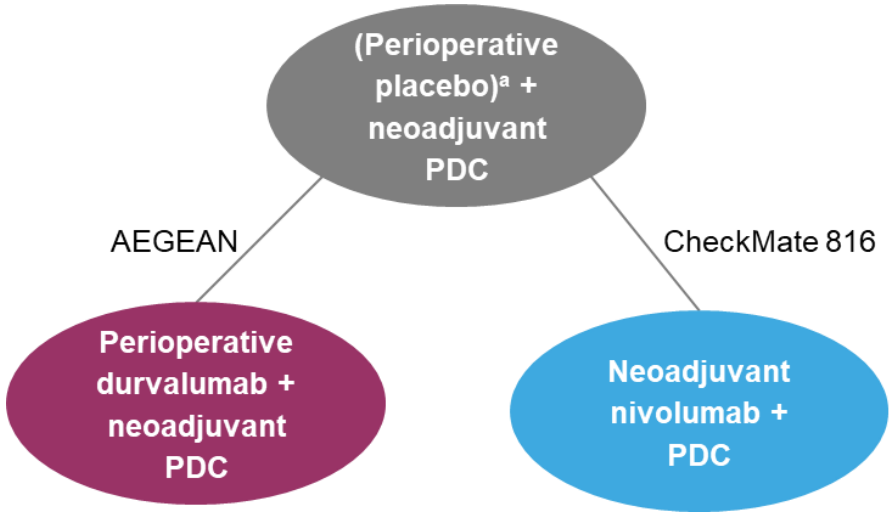
Population	NMA Analysis	Exclusions
mITT	Base-case	NA
mITT	Sensitivity analysis 1	Exclude studies with 2G chemotherapy
mITT	Sensitivity analysis 2*	Exclude studies with stage III patients only
mITT	Sensitivity analysis 3	Exclude Asia only studies
mITT	Sensitivity analysis 4	Exclude studies for any of the reasons above

Back to clinical effectiveness slide

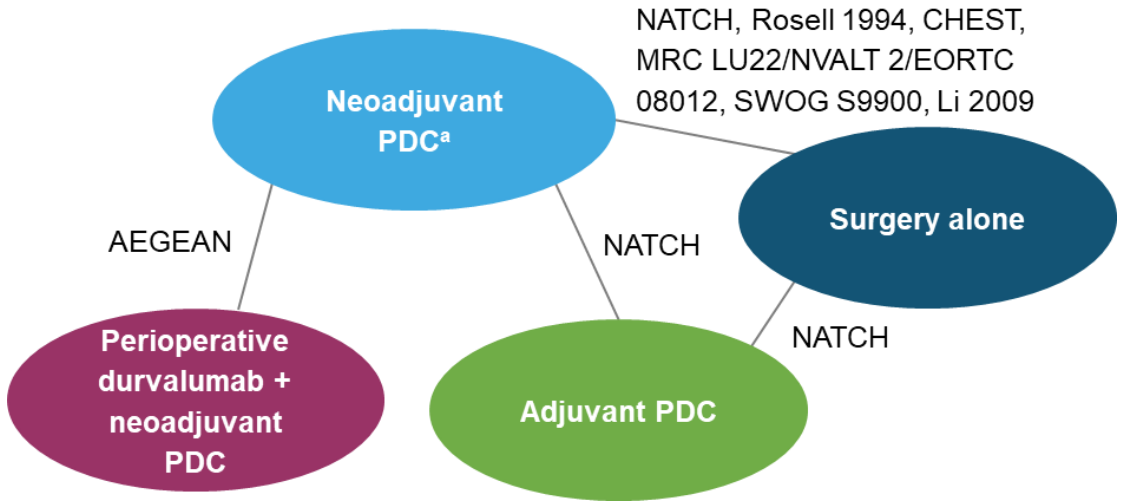
Abbreviations: ITC, indirect treatment comparison; MAIC, matching adjusted treatment analyses; mITT, modified intention to treat; NMA, network meta-analyses

NMA/ITC network diagram(s)

Anchored MAIC



NMA



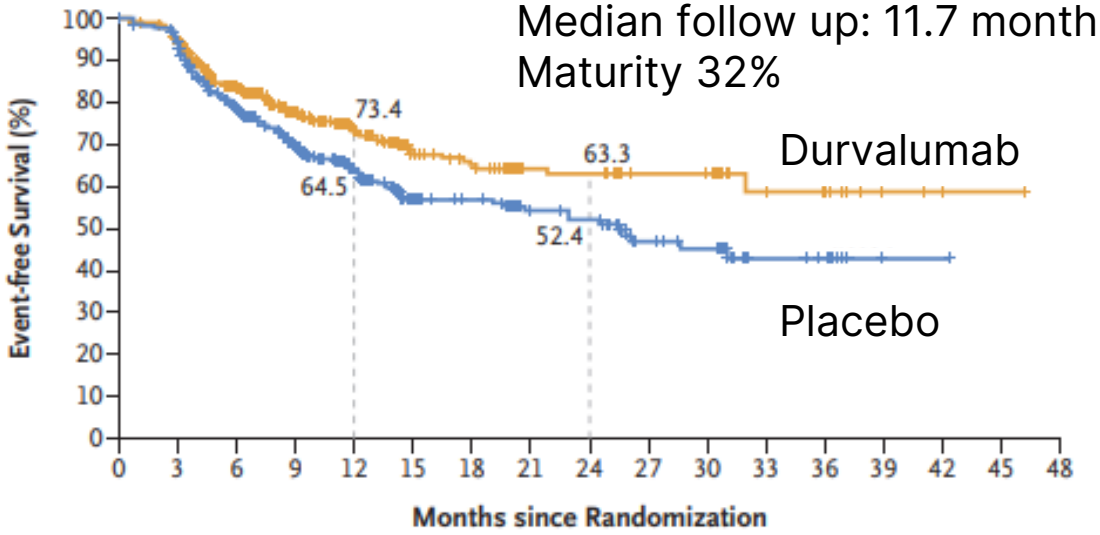
Back to clinical effectiveness slide

Abbreviations: ; ITC, indirect treatment comparison; MAIC, matching adjusted treatment analyses; NMA, network meta-analyses; PDC, platinum-doublet chemotherapy

Clinical trial results (AEGEAN)

EFS

Median follow up: 11.7 months
Maturity 32%

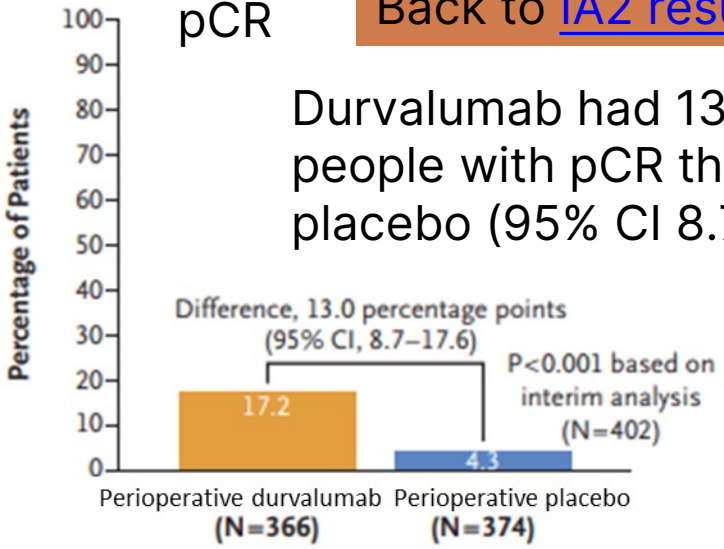


No. at Risk

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

Intervention	Events/patients (%)	Median EFS (95%CI)
Perioperative durvalumab	98/366 (26.8)	NR (31.9 to NR)
Perioperative placebo	138/374 (36.9)	25.9 (18.9 to NR)
HR (95% CI)		0.68 (0.53 to 0.88)

pCR



Durvalumab had 13% more people with pCR than placebo (95% CI 8.7 to 176)

Back to IA2 results slide

[redacted]

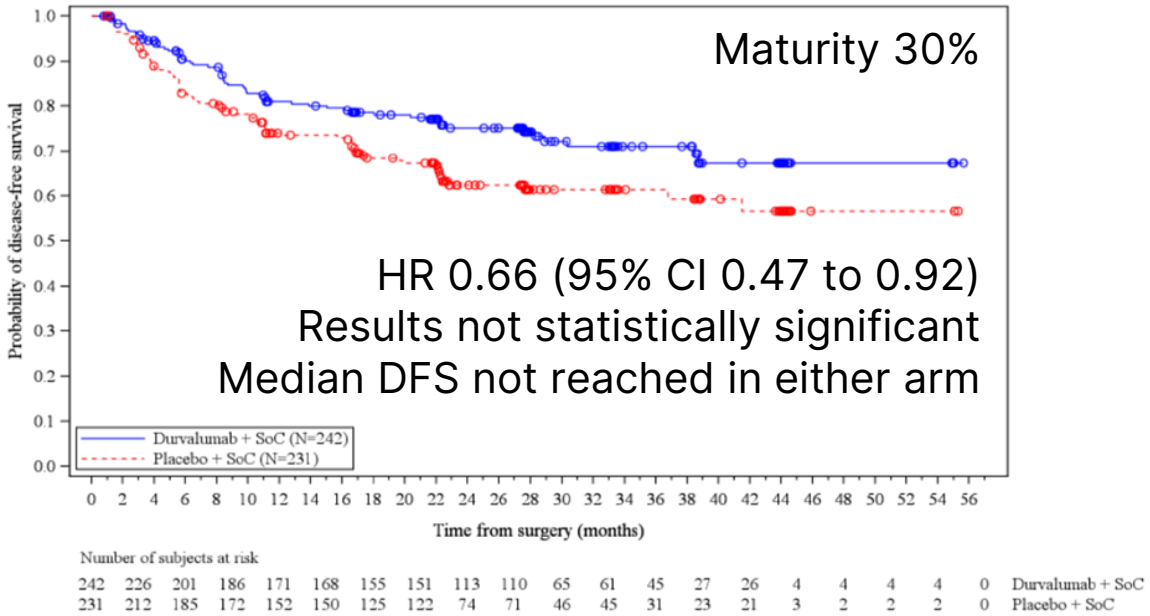
NICE

Abbreviations: EFS, event-free survival (progression before surgery, recurrence after surgery or death); pCR, pathologic complete response (absence of tumour cells in surrounding tissue and lymph node samples taken at surgery); NR, not reached; CI, confidence intervals; HR, hazard ratio; OS, overall survival; HR, hazard-ratio

EAG critique of updated AEGEAN (IA2) results

Back to IA2 results slide

DFS (results reported for first time)



Endpoint	EAG comment
DFS	• Clear advantage to perioperative durvalumab, maintained at 36 months
HRQoL	• Updated EORTC QLQ-C30 data continued to show no clinically meaningful difference between the treatment arms • After week 4 and until the latest follow-up of week 44, the values for the placebo arm showed a slight advantage
Adverse events	• Minimal difference in summary statistics between the 2 DCOs

Abbreviations: CI, confidence intervals; DCO, data cut off; DFS, disease-free survival; EFS, event-free survival (progression before surgery, recurrence after surgery or death); HR, hazard ratio; HRQoL, health-related quality-of-life; IA, interim analysis; OS, overall survival

Back to ITC results slide

Updated clinical effectiveness results – MAIC

		Original company submission			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]

Base case = weighting based on all possible effect modifiers as recommended by NICE DSU TSD18 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 company submission, ECOG only in additional evidence.

EAG comments

- Results of the MAIC were largely unchanged between EFS IA1 and IA2 analyses

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; HR, hazard ratio; IA, interim analysis; LCL, lower control limit; MAIC, match-adjusted indirect comparison; PDC, platinum-doublet chemotherapy; UCL upper control limit

Back to time-varying HRs slide

Time-varying hazard ratio methods

Choice of distribution - EFS HRs for perioperative durvalumab vs neoadjuvant nivolumab over time – fixed effect model

- Log-normal was second best fitting but allowed for more flexibility in the hazards so selected by company
- Other distributions provided as scenarios

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

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

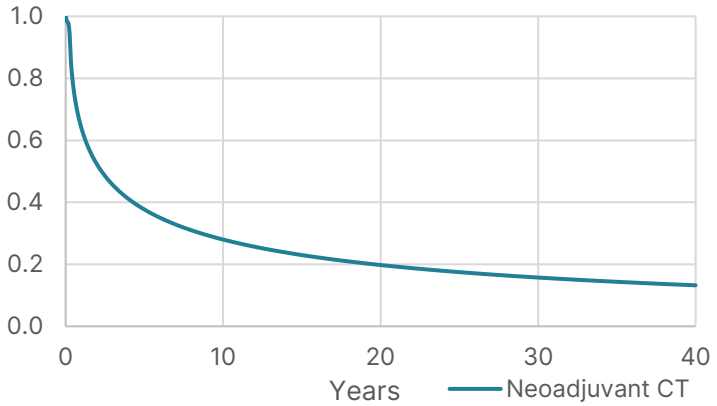
Abbreviations: AIC; Akaike information criterion; EFS, event-free survival; HR, hazard ratio; mITT, modified intention to treat

Time-varying hazard ratio versus neoadjuvant chemotherapy

Time-varying hazard ratios (versus neoadjuvant chemotherapy)

Company's model overview – Modelling efficacy at EFS

EFS to LRR and DM (TP1-2)



Piecewise neoadjuvant CT EFS reference curve, censored for death (3 months AEGEAN KM, then lognormal)

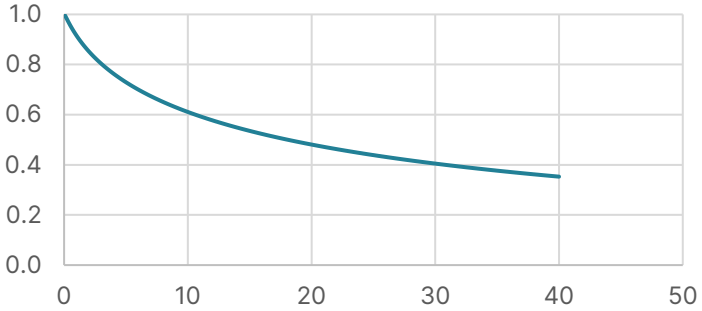
Hazard ratios from CM-816, MAIC and NMA applied (see ITC slide)

Or time-varying hazard ratio scenario

[redacted]

Per cycle transition probabilities generated for each intervention for EFS to LRR and DM

EFS to death (TP3)



Pooled EFS to death curve from AEGEAN extrapolated with lognormal distribution

Per cycle transition probabilities generated for each intervention for EFS to Death

EFS to death modelled for each comparator

Back to model overview

Abbreviations: EF, event free; LRR, loco-regional recurrence; DM, distant metastases; TP, transition probability