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

Technology appraisal committee A [9th July 2024]

Contains redacted information

Chair: James Fotheringham

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Company: AstraZeneca

Perioperative durvalumab for treating resectable non-small-cell lung cancer

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on non-small-cell lung cancer (NSCLC)

A common cancer and leading cause of cancer-related deaths in the UK

Epidemiology

- Approximately 34,000 new cases of lung cancer diagnosed annually
- 80-85% of lung cancer estimated to be NSCLC

Diagnosis and classification

- Often diagnosed at advanced/metastatic stage. NHS TLHC program aims to diagnose earlier
- Classified by histology or presence of biomarkers (driver mutations or PD-L1 expression)
- AJCC/UICC criteria stage lung cancer from 1A to 4B based on TNM criteria

Symptoms and prognosis

- Early stages may be asymptomatic, later symptoms include dyspnoea, fatigue and cough
- Curative intent surgery used for early/locally advanced NSCLC but recurrence is common
- 5-year survival is 63% (stage 1), 41% (stage 2), 16% (stage 3) and 4% (stage 4)

Abbreviations: PD-L1, programmed cell death 1 ligand; AJCC, American joint committee on cancer; UICC, union for international cancer control; TNM, tumour/node/metastasis staging; TLHC, targeted lung health check

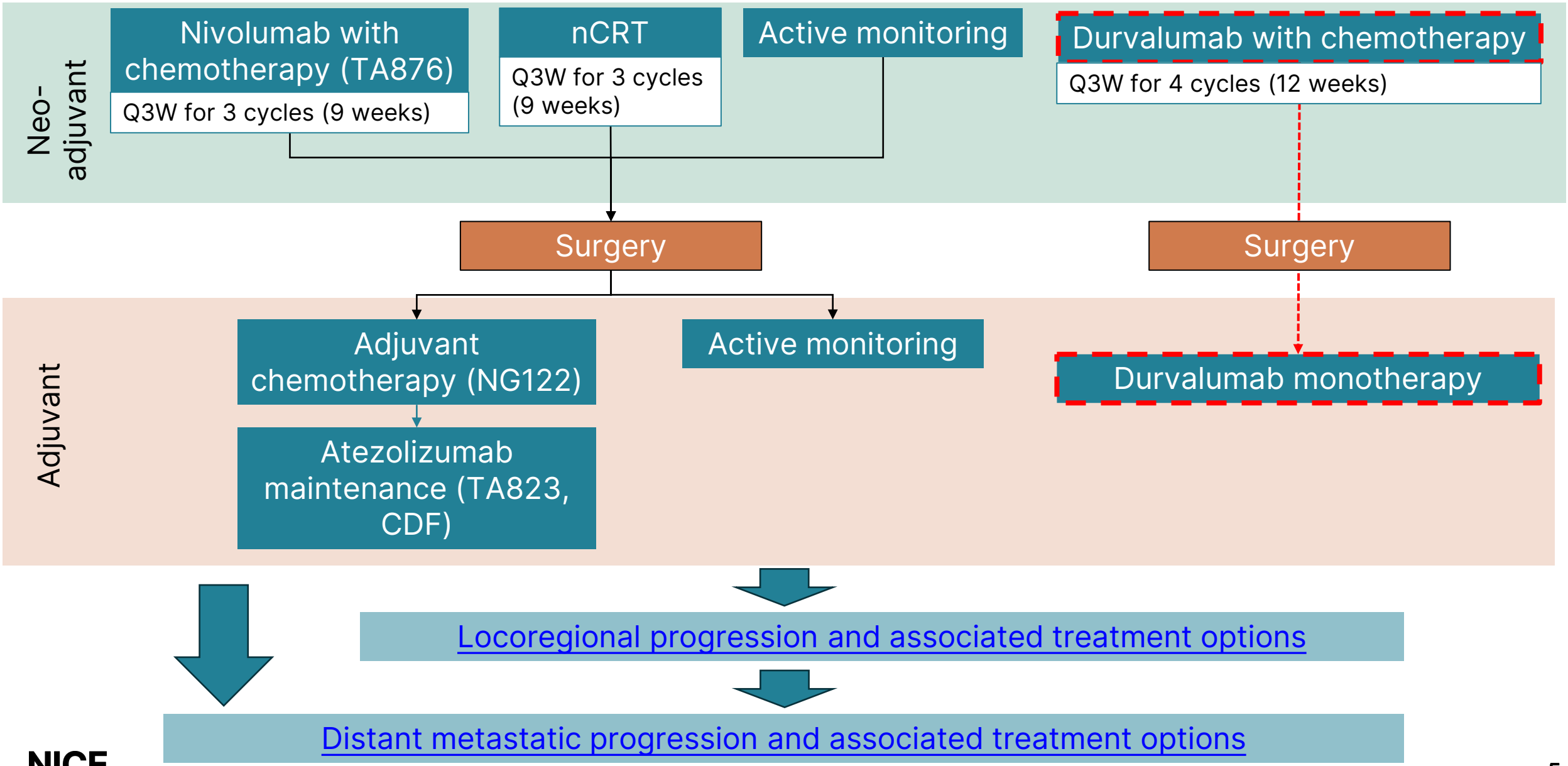
Patient perspectives

Submissions from Roy Castle Lung Cancer Foundation

- Relapse after surgery means that further curative therapy is unlikely
- There is a need to develop therapy options to reduce the risk of recurrence after lung cancer surgery
- Nivolumab with chemotherapy recommended in March 2023, there is a need to explore additional therapies to improve outcomes and reduce recurrence
- Patients and carers want the chemoimmunotherapy with the best outcomes
- Important that decision to have neoadjuvant treatment before surgery does not mean the window for successful surgery is missed (delays in assessment and administration of neoadjuvant treatment could result in disease progression that precludes surgery)

"Patients and carers have continual anxiety that the lung cancer will come back"

Treatment pathway (resectable NSCLC)



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

Durvalumab (Imfinzi, AstraZeneca)

	Durvalumab treatment info
Marketing authorisation	• [redacted]
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 combined with chemotherapy in the neo-adjuvant phase to prime the immune system and slow tumour growth and used 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

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

Key issues

Issue	Resolved?	ICER impact
Comparators: inclusion of nCRT and definition of active monitoring	No	Small
Issues and inconsistency with the indirect treatment comparison	No	Unknown
Clinical trial generalisability to NHS clinical practice	No	Unknown
Limited reporting and indirect comparison of key outcomes	No	Unknown
Modelling of cure	No	Moderate to large
Proportional hazards assumption, time dependent hazard ratios and treatment effect waning	No	Potentially very large
Transitions from LRR and DM health states (model cycle vs time in health state)	No	Unknown
Utility values in the model	No	Small
Assumptions around BSC (only transition to death state)	No	Small
Proportion of people eligible for IO in LRR and DM health states and effectiveness of IOs upon retreatment	No	Unknown
Probability of an EFS event being to LRR or DM (and time and treatment independence)	No	Small

 Large impact on ICERs

 Small impact on ICERs

 Unknown impact on ICERs

NICE Abbreviations: LRR, locoregional recurrence; DM, distant metastases; nCRT, neoadjuvant chemoradiotherapy; BSC, best supportive care; EFS, event free survival; IO, immuno-oncology treatment; ICER, incremental cost-effectiveness ratio

Key issues: Comparators

Small impact on ICERs

Background

- Neoadjuvant nivolumab, adjuvant chemotherapy and surgery alone (proxy for active monitoring) modelled.
- Neoadjuvant chemoradiotherapy was in scope but not modelled.

Company

- Only a small portion (~7%, who are Stage 3A, N2) would have nCRT. This stage contains both resectable and unresectable disease so. Did not consider a relevant comparator.
- Surgery alone considered the only relevant representation of active monitoring where no systemic therapy given

EAG comments

- Unclear if surgery alone is a proxy for active monitoring
- EAG's clinical expert agreed nCRT not a valid comparator, as population slightly different to that of AEGEAN
- EAG considers this does not mean it is inferior to perioperative durvalumab and therefore should be modelled
- Require more information on source of statement that surgery alone is only representation of active monitoring

Tech team considerations – (*for information*)

- In TA876 (neoadjuvant nivolumab for NSCLC) surgery alone considered a proxy for active monitoring and nCRT modelled as comparator. Committee concluded that the included comparators were appropriate
- The ICERs for neoadjuvant nivolumab versus nCRT and adjuvant chemotherapy were similar

Is surgery alone a suitable proxy for active monitoring?
Are the comparators modelled in this appraisal appropriate?

Abbreviations: nCRT, neoadjuvant chemoradiotherapy; ICER, incremental cost-effectiveness ratio; N2, two lymph nodes involved

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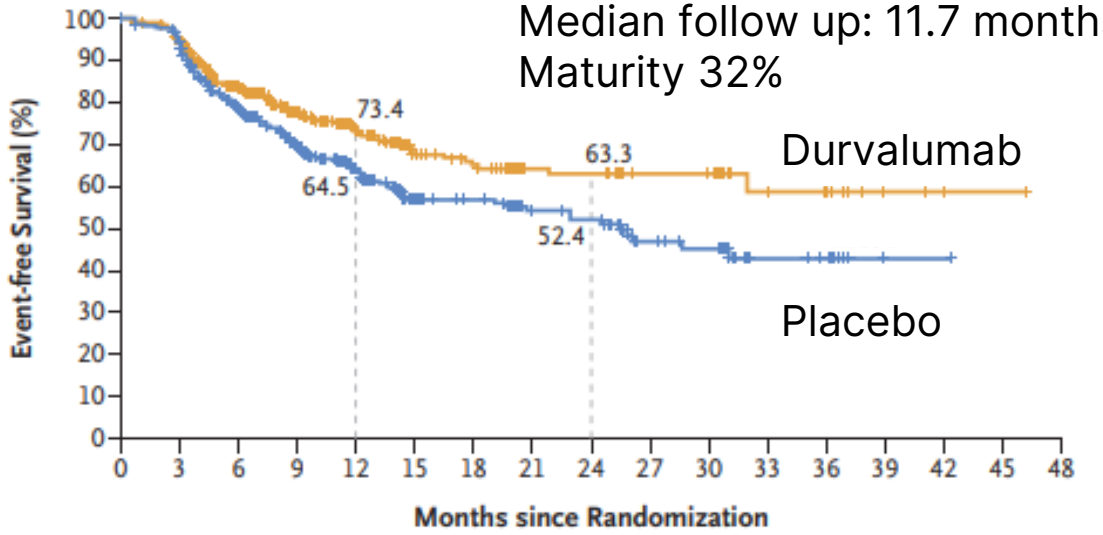
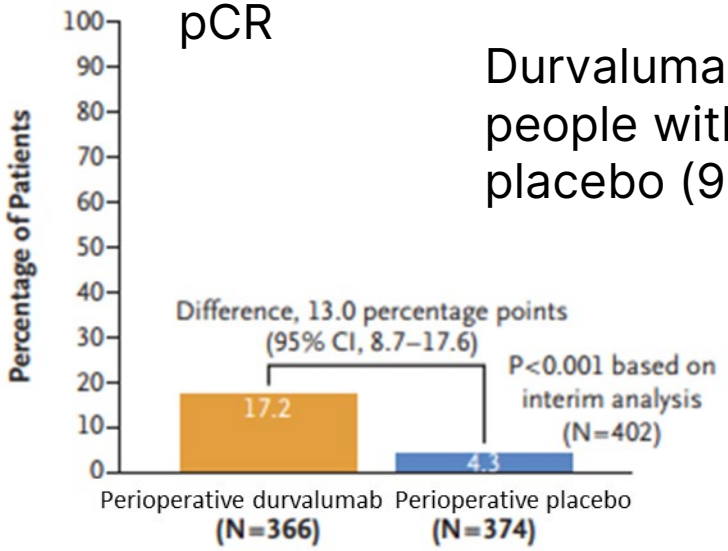
Clinical trial results (AEGEAN)

EFS



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)

[redacted]

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

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

EFS hazard ratios (MAIC & NMA) versus neoadjuvant chemotherapy (model driver)

Intervention/comparator	Source	HR 95%CI
Perioperative durvalumab	MAIC (3-month+, base case) adjusted sample	[redacted]
Perioperative durvalumab	Unadjusted (3-month)	[redacted]
Neoadjuvant nivolumab + chemotherapy	Checkmate 816	[redacted]
Adjuvant chemotherapy	NMA (sensitivity analysis 2)	[redacted]
Surgery alone	NMA (sensitivity analysis 2)	[redacted]

ITC methods | ITC networks | More ITC results

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

Key issues: Issues with the ITCs

? Unknown impact on ICERs

Background

- ITC analyses disjointed. MAIC to compare against neoadjuvant nivolumab and an NMA to other comparators
- AEGEAN trial is adjusted to match CheckMate-816, adjusted MAIC sample compared to neoadjuvant chemo.
- No population adjustment is made to the comparisons with adjuvant chemotherapy and surgery alone.
- Heterogeneity of treatments across studies in the NMA and a lack of consistency modelling conducted

EAG comments

- A multi-level network meta-regression could have been used to conduct an all-encompassing NMA
- There was a closed loop in the NMA which could have been used for consistency modelling

Company

- MAIC considered superior for comparison versus nivolumab as has fewer assumptions and was more flexible
- Insufficient reported info on baseline characteristics to perform MAICs for non-IO comparisons so NMA used with sensitivity analyses to explore heterogeneity
- Considered that consistency modelling was not feasible due to absence of a direct/indirect evidence loop

NICE technical team considerations

- Estimates of cost-effectiveness suggest the comparison with nivolumab is the most important in terms of risk of decision error

Are the indirect treatment comparisons appropriate for decision making?

NICE

Abbreviations: ITC, indirect treatment comparison; NMA, network meta analysis; MAIC, matching adjusted indirect comparison; IO, immuno-oncology treatment; STC, simulated treatment comparison

Key issues: Generalisability to UK population

? Unknown impact on ICERs

Background

- Subgroup analyses from AEGEAN revealed certain characteristics may be treatment effect modifiers
- EFS: sex and smoking status; pCR: PD-L1 expression, lymph node station, disease stage and smoking status

EAG comments

- No data provided comparing trial population to UK practice population for potential effect modifiers. generalisability of trial and analysis to UK therefore uncertain

Company

- UK target population is aligned with expected license for perioperative durvalumab
- Advisory board confirmed AEGEAN was generalisable to UK population (differences in % of males, squamous disease and lymph node station however did not consider these a generalisability concern)

Other considerations – (*for information*)

- Committee in TA876 (neoadjuvant nivolumab for NSCLC) considered that there were differences in demographics between the trial and NHS clinical practice but concluded that the clinical evidence from CheckMate-816 was uncertain but suitable for decision making.
- Summary of key baseline characteristics considered to be effect modifiers presented on next slide

Is the AEGEAN trial generalisable to NHS clinical practice?
Is the adjusted AEGEAN trial sample generalisable to NHS clinical practice?

Abbreviations: pCR, pathologic complete response; PD-L1, programmed cell death ligand 1;

Baseline characteristics*

Characteristic	AEGEAN	Checkmate-816	AEGEAN (MAIC base case)	National Lung Cancer Audit 2024 (England)
Sex female %	28.4	28.8	[redacted]	49.8Δ
Never smoker %	14.5	10.9	[redacted]	9.5Δ
Stage 2 %	28.9	Not reported	[redacted]	28%Δ
Stage 3a %	45.7	57.4	[redacted]	41%Δ
Stage 3b %	25.3	12.1	[redacted]	31%Δ‡
PD-L1 <1% (%)	33.4	46.5	[redacted]	?
PD-L1 1-49% (%)	37.43	30.5	[redacted]	?
PD-L1 ≥50% (%)	29.2	24.0	[redacted]	?
Lymph node 0 %	28.7	Not reported	[redacted]	?
Lymph node 1 %	21.9	Not reported	[redacted]	?
Lymph node 2 %	49.5	Not reported	[redacted]	?
Median age (years)	65	64	[redacted]	74Δ

Abbreviations: PD-L1, programmed cell death ligand 1; MAIC, matching adjusted indirect comparison;
*Only characteristics which EAG considered to be important effect modifiers for EFS and pCR (excluding geographic region) shown
Δ Figures extracted from National Lung Cancer Audit state of the nation report 2024 and reweighted to match decision problem for stage
‡ This figure in the NLCA data is for Stage 3B/C so reasonable to expect the figure for 3B alone would be lower

Key issues: Limited reporting and comparison of outcomes

Background

- No results were provided for DFS, and EFS was the only outcome analysed in an ITC with the comparators and it is the main driving force behind the cost-effectiveness estimates in the model
- HRQoL was not subject to an ITC, if it was found to be different to the comparators then it may be necessary to model treatment dependent utilities which could affect the estimates of cost effectiveness

Company

- DFS not presented as per trial MTP (DFS to be formally assessed when EFS data is at 40% maturity).
- EFS a more relevant outcome as can evaluate the full perioperative approach and is a surrogate outcome for OS.
- Changes in HRQoL in the AEGEAN trial were not different between durvalumab and placebo

EAG comments

- Raw DFS data could have been provided without formal statistical analysis as reassurance for committee
- Other outcomes in scope should be compared in ITC. Superiority cannot be inferred from EFS alone.
- Consider that a relative increase in QoL would be expected from durvalumab. HRQoL should be included in the ITC so that any differences between durvalumab and comparators can be included in the modelling

Other considerations (*for information*)

- ITCs for TA876 compared EFS, OS, TTLR, TTDM, pCR and safety. But did not include HRQoL.
- Utility values were health state specific, not treatment specific. Committee considered this a minor issue.

Are the outcomes reported and compared in the ITC sufficient for decision making?

Abbreviations: DFS, disease free survival; EFS, event free survival; ITC, indirect treatment comparison; MTP, multiple testing procedure; OS, overall survival; HRQoL, health related quality of life;

Perioperative durvalumab for treating resectable NSCLC

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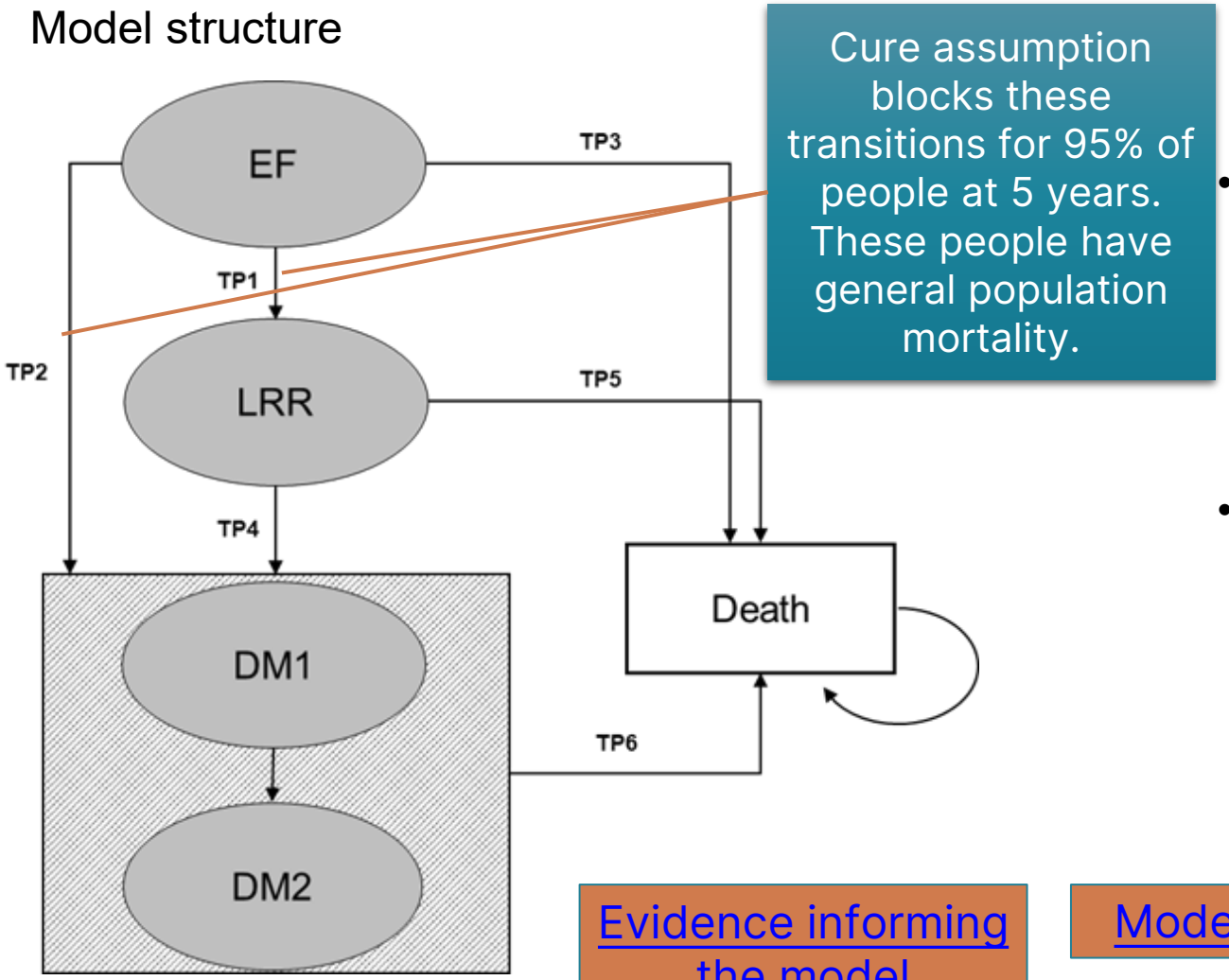
Company's model overview

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

Evidence informing the model

Modelling of EFS

Modelling of DM

Modelling of LRR

Abbreviations: EF, event free; LRR, loco-regional recurrence; DM, distant metastases; TP, transition probability; HR, hazard ratio; ICER, incremental cost-effectiveness ratio

Key Issue: Cure (appendix)

Large impact on ICERs

Background

- Model assumes 95% of people in EFS state at 5 years considered cured and have general population risks.
- Cure proportion and timepoint assumptions based only on clinical opinion. Total proportions not validated.

CS Base case	Durvalumab	Nivolumab	Adjuvant PDC	Surgery alone
Model proportion cured	[redacted]	[redacted]	[redacted]	[redacted]

Company

- Clinical advisory board considered 5-year timepoint reasonable, recurrence after this point would be <10%
- Timepoint and proportion aligns with TA876, TA823 and TA761 (EGFRm+ NSCLC)

EAG comments

- Recall EAG position from TA876: no convincing evidence to support how cure assumption modelled
- Requested scenarios to explore different cure points and proportions which were not conducted by company
- Has included a base case both with and without cure modelled and considers both potentially plausible

Are the total proportions of people cured for each intervention plausible?
What is the most appropriate cure point and proportion for decision making?

Abbreviations: EFS, event-free survival; EGFRm+, epidermal growth factor receptor mutation positive;

Key Issue: PH assumption and treatment effect waning (appendix)

Background

- Proportional-hazards assumed for all comparisons with neo-adjuvant CT from 3 months. Time dependent hazard-ratios might be more efficient and a parametric NMA could be used (Cope et al 2020, used in TA865)
- EFS HRs are a key driver of estimates of cost-effectiveness.

Company

- Fitting survival distributions to overall trial period from AEGEAN resulted in poorly fitting curves.
- Consider the 0-3 month and 3 month plus piecewise approach is appropriate.
- In TA876, clinicians validated EFS long-term projections (constant HR) for neoadjuvant nivolumab and PDC

EAG comments

- Poor fit of survival distributions is an issue but assuming a fixed hazard-ratio for most of the time horizon might be more of a problem (especially as hazard plots show differences over time)
- EAG requested scenarios around treatment effect waning. Company declined no data to inform them.
- Ignores possibility of treatment effect waning. Explored in scenario which limits model time horizon to 5 years.

Other considerations – Previous appraisals (*for information*)

- TA823: Separate parametric models fitted to each treatment arm (DFS) – No additional waning modelled
- TA876: Joint parametric models with intervention (nivolumab) arm as predictor – No additional waning modelled
- TA851: (TNBC) Separate parametric models fitted to each treatment arm (EFS) – No additional waning modelled

Is it appropriate to apply a time-constant hazard ratio to estimate EFS for the lifetime of the model?

Abbreviations: PH, proportional hazards; HR, hazard ratio; NMA, network meta-analysis; CT, chemotherapy; PDC, platinum doublet chemotherapy; triple negative breast cancer; EFS, event-free survival; DFS, disease-free survival; TA823 adjuvant maintenance atezolizumab for NSCLC; TA851, perioperative pembrolizumab for triple negative breast cancer

Key Issue: Time independent TPs in LRR/DM (appendix)

Background

- Transition probabilities in the LRR and DM states are “model cycle” specific and not “time in state” specific. (e.g someone entering LRR in cycle 30 has TPs relevant to cycle 30 in that health state, and not cycle 1)
- This could bias the estimates of cost-effectiveness given that transition probabilities vary over time.

Company

- Model-cycle approach is common practice and maintains simplicity & transparency in absence of IPD
- Setting exponential distributions for PFS & TTD emulates constant TPs but exponential has poor fit to data

EAG comments

- Transition probabilities should be implemented as a function of the time since entry into the LRR or DM health states rather than as a function of model cycle. Using the latter might bias estimates of cost-effectiveness.
- Company declined to elaborate on implications and explore at clarification. Direction and extent of bias unclear.

Other considerations (*from previous appraisals, for information)*

- TA761: “LRR, DM1 and DM2 are intermediate health states represented by sub-models which use tunnel states to allow event risks to be dependent on the time since model entry”
- TA823: Transition probability of LRR and DM events time invariant.
- TA876: Time invariant transition probability from LR to DM (expert opinion)

Is using health state occupancy time independent transition probabilities for LRR and DM appropriate for decision making?

Abbreviations: LRR, locoregional recurrence; DM, distant metastases; TP, transition probabilities; PFS, progression free survival; TTD, time to discontinuation; IPD, individual patient data; TA761, adjuvant osimertinib for EGFR+ NSCLC; TA823, adjuvant maintenance atezolizumab for NSCLC; TA876, neoadjuvant nivolumab for NSCLC

Key Issue: Utility data in the model

Small impact on ICERs

Background

- EF utility informed only by neoadjuvant period of AEGEAN and is higher than UK general population utility
- ≥20% missing HRQoL data could bias EFS utility estimate

Scenario	EF	LRR	DM1	DM2
Company base case	[redacted]	[redacted]	0.759	0.662
UK population scenario	0.829	[redacted]	0.759	0.662
Company scenario	0.72	[redacted]	0.759	0.662
EAG 0.2 decrement scenario	0.829	[redacted]	[redacted]	[redacted]
TA823	0.80	0.77	0.71	0.69
TA761 (EGFRm+ disease)	[redacted]	[redacted]	[redacted]	0.640

Company

- Acknowledge potential implications (over/ underestimation) of only using AEGEAN neoadjuvant utility data but was not possible to use adjuvant period data due to collection limitations
- Impact assessment of missing HRQoL data challenging, included scenario with 0.72 EFS utility to explore issue

EAG comments

- Concern over basing utility on neoadjuvant period only (questionable utility estimates) and missing data in MMRM model (could overestimate EFS utility if patients with worse HRQoL less likely to respond)
- Company scenarios don't adjust subsequent states relative to EFS. Provide additional scenario exploring 0.2 utility decrement from EF to LRR maintaining absolute decrement from LRR to DM1 and DM2

Other considerations (patient expert testimony)

- The utility values in the company base case reflect the patient expert's experience with NSCLC

Are the utility estimates from AEGEAN plausible?
Which utility set should be used for decision making?

Abbreviations: HRQoL, health related quality of life; EF, event-free; EFS, event-free survival; MMRM, mixed model for repeated measures; LRR, locoregional recurrence; DM distant metastates

Key Issue: Assumptions around best-supportive care

Small impact on ICERs

Background

- Model assumes that people having BSC in the LRR state can only transition to death state.

Company

- Simplifying assumption made in line with TA823 and deemed appropriate by clinical expert advisory board
- Clinical expert noted that life expectancy in the LRR state for BSC would be less than 6 months

EAG comments

- Unclear whether this assumption is clinically plausible or why it was required
- Durvalumab would have a lower number of people in the LRR state (due to EFS HR) and would therefore be affected less by this assumption than comparators.
- Clinical expert considered this too strong an assumption; some people would develop metastatic disease
- Requested clarification scenarios to explore impact of assumption which were not carried out by company
- EAG scenario explores no BSC in LRR (people redistributed over active treatments)

Is the simplifying assumption that people having BSC in the LRR state can only progress to the death state suitable for decision making?

Abbreviations: BSC, best supportive care; LRR, locoregional recurrence; EFS, event free survival; hazard ratio

Key Issue: Retreatment with immunotherapies

Background

- Base case: retreatment permitted if progression 6 months or more after finishing EFS IO treatment.
- 70% of people at LRR (TA798 RIA) and 80% of people at DM (TA683 & TA770) assumed eligible for IO
- No change in effectiveness of IOs when used as retreatment in later lines was modelled
- Note: no retreatment restriction at DM for those who had an IO at LRR (regardless of time to progression)

Company

- Scenarios exploring 12-month retreatment restriction and emulating 6-month retreatment restriction for people having IO at LRR (i.e people progressing on cCRT + durvalumab at LRR not eligible for IO treatment in DM)
- Acknowledge that the model implicitly assumes that the efficacy of IOs does not diminish with retreatment

EAG comments

- Submitted additional scenario exploring 50% of people at LRR and DM being eligible for IO treatment
- Consider that it is plausible that the effectiveness of IOs might be reduced upon retreatment and note that this has not been modelled or explored in any scenarios (scenario was requested at clarification)
- Durvalumab has fewer people in LRR/DM at a given time so diminishment of treatment effect could drive ICERs

Is modelling a retreatment restriction of 6 months appropriate?
Is it appropriate to assume that effectiveness of IOs does not diminish upon retreatment?
Are the proportions of people eligible for immunotherapy in the LRR and DM health states appropriate for decision making?

Abbreviations: RIA, resource impact assessment; EFS, event-free survival; IO, immuno-oncology treatment; LRR, locoregional recurrence; cCRT, concurrent chemoradiotherapy; ICER, incremental cost-effectiveness ratio

Key Issue: Probability of an EFS event being LRR or DM

Background

- Probability of EFS event being LRR ([redacted]) or DM ([redacted])assumed constant and treatment independent (based on clinical expert opinion)
- The equivalent proportions in the AEGEAN trial were LRR ([redacted]and DM ([redacted])

EAG comments

- Constant probabilities inconsistent with clinical opinion provided to the EAG
- Requested scenario analyses to investigate time and treatment dependent proportions going to LRR and DM which company did not conduct

Company

- Modelling of constant proportions to LRR and DM conducted in line with clinical expert advisory board advice
- Acknowledge potential for treatment dependent transition probabilities to LRR and DM but note lack of evidence
- No evidence to support conducting scenario analyses to explore time and treatment dependent transitions

Is the modelling of the proportion of EFS events which are LRR and DM appropriate for decision making?
Is it appropriate to assume that these proportions are time and treatment independent?

Abbreviations: EFS, event-free survival; LRR, locoregional recurrence; DM, distant metastases

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Parameter	Company base case	EAG base case
AE disutility error	-	Corrected error in implementation of AE disutility
Cure assumption	Cure modelled 95% at 5 years	One base case with cure as per company base case One base case with cure removed
EFS Utility value	EFS utility higher than matched general population level	EFS utility capped at general population
Wastage	No wastage costs applied for IV chemotherapy	Apply wastage costs via company “no vial sharing” scenario

Additional scenarios

Parameter	Base case	Scenario
BSC transitions	BSC only transitions to death state	No BSC in LRR (explores impact of BSC transitions)
Treatment effect (EFS)	Constant for whole time horizon	5-year model (emulates 5 year treatment effect)
IO eligibility at LRR/DM	IO eligibility: LRR: 70%, DM 80%	50% IO eligibility in both LRR and DM
EFS utility	Higher than general population	Apply 0.2 utility decrement to EFS for LRR utility
IO Retreatment	6 months restriction	12 months restriction

Abbreviations: AE, adverse events; EFS, event free survival; BSC, best-supportive care; LRR, locoregional recurrence; DM, distant metastatis; IO, immuno-oncology treatment; IV, intravenous; BSC, best-supportive care;

Cost-effectiveness

Due to the presence of confidential comparator discounts all decision making ICERs have been presented in Part 2 slides for committee consideration.

Abbreviations: ICER, incremental cost-effectiveness ratio

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.
- When are further data-cuts from the AEGEAN trial expected for various outcomes?

Equality considerations

No equalities issues were raised during the course of this appraisal

Perioperative durvalumab for treating resectable NSCLC

Supplementary appendix

- Additional key issues
- Background
- Clinical effectiveness
- Cost-effectiveness

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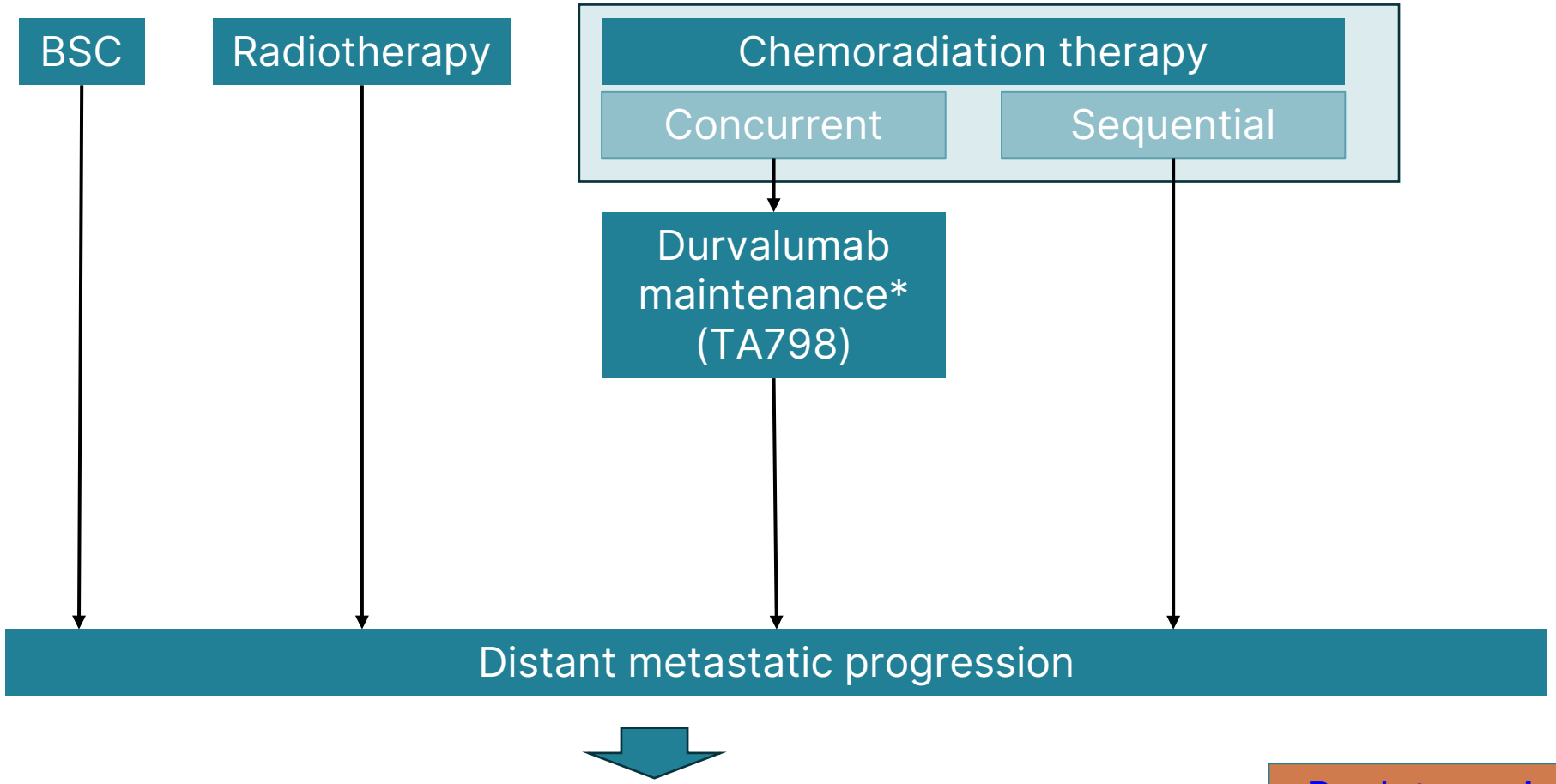
Treatment pathway

Unresectable locally advanced



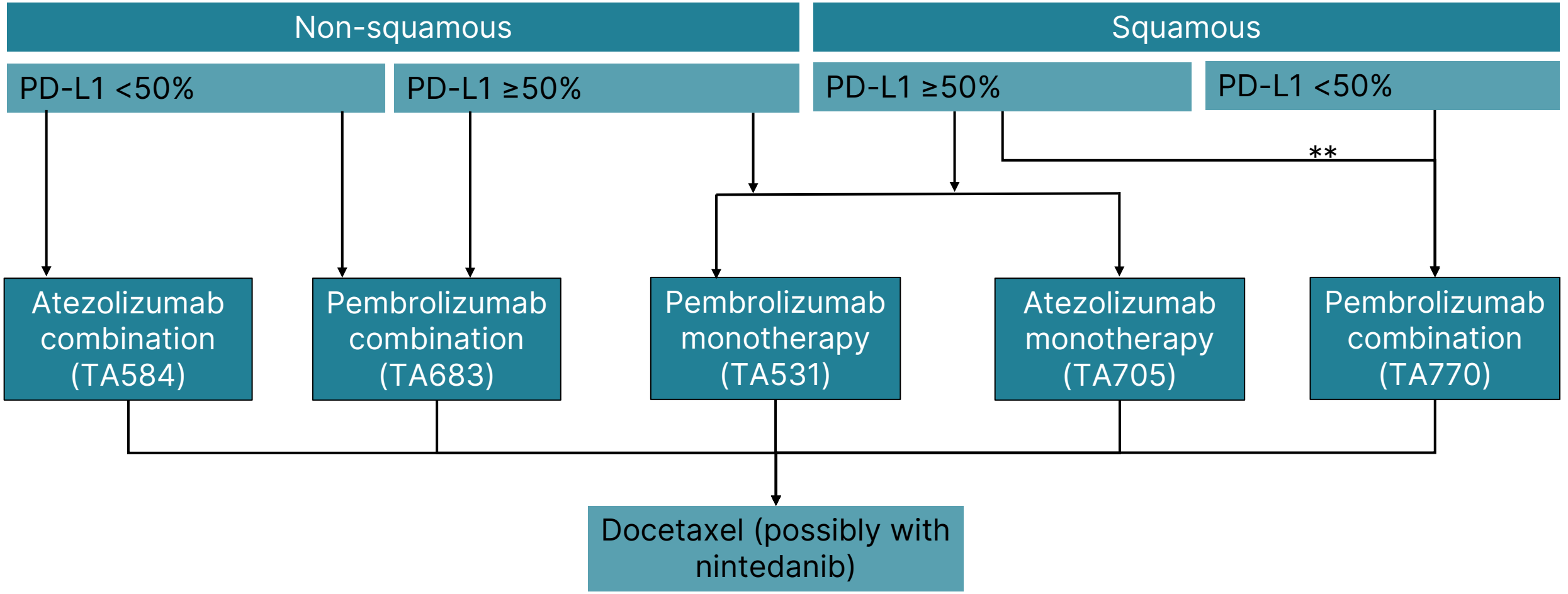
Back to main treatment pathway

Abbreviations: CDF, cancer drugs fund; BSC, best supportive care; PD-L1, programmed cell death ligand 1

*Durvalumab maintenance recommended for PD-L1 positive NSCLC

Treatment pathway (active treatments*)

Advanced/metastatic



Back to main treatment pathway

Abbreviations: CDF, cancer drugs fund; PD-L1, programmed cell death ligand 1

*Chemotherapy only regimens or BSC is also offered where immunotherapy or active treatment is not suitable or preferred

** Only where urgent clinical intervention is required

Adverse events

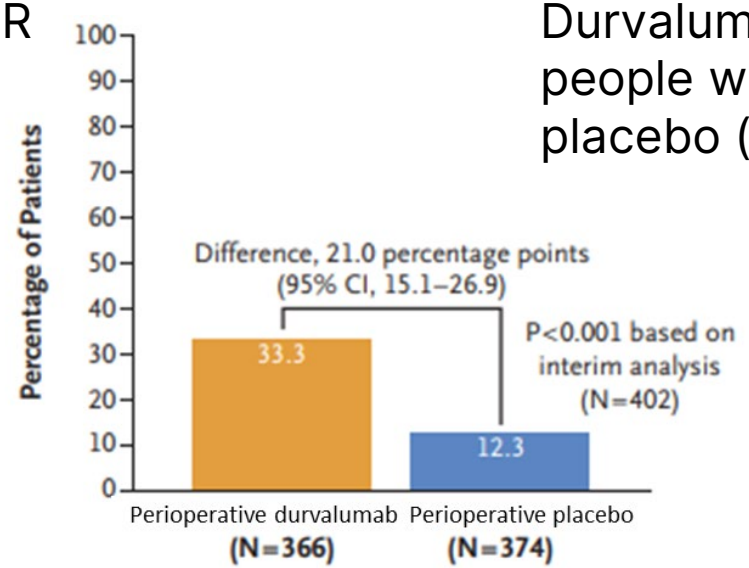
Perioperative durvalumab generally well-tolerated

- Company consider that perioperative durvalumab was well-tolerated with manageable adverse events in AEGEAN trial
- EAG consider this statement was upheld to a large extent by the results of the trial
- However note that there was a greater risk of “deaths possibly related to any study treatment” in perioperative durvalumab compared to perioperative placebo
- Informal analysis (AEGEAN statistical analysis plan did not include formal testing for AE results) by the EAG reported that the relative risk was 3.47 (95% CI 0.73 to 16.62) and EAG considered that while this was likely due to sampling error there was a possibility that perioperative durvalumab was associated with a greater risk of death due to treatment given than perioperative placebo.
- EAG: “The clinical significance of these adverse results, albeit uncertain, should therefore be weighed up against the benefits by the committee”

Abbreviations: CI, confidence intervals; AE, adverse events

Clinical trial results (ii)

MPR



Durvalumab had 21% more people with MPR than placebo (95% CI 8.7 to 176)

ORR

Response	Durvalumab n=366	Placebo n=374
ORR, n (%)	206 (56.3)	142 (38.0)
95% CI	51.0-61.4	33.0-43.1
Complete response, n (%)	4 (1.1)	1 (0.3)
Partial response, n (%)	202 (55.2)	141 (37.7)
Stable disease, n (%)	124 (33.9)	189 (50.5)
Progression, n (%)	11 (3.0)	15 (4.0)
Not evaluable, n (%)	25 (6.8)	28 (7.5)

[redacted]

<u>OS from D120SU</u>

Median OS not reached for either intervention.

HR (95% CI): [redacted]

Data maturity: 29%

EAG comment: OS only outcome where the D120SU (August 2023) used. Other outcomes relied on older November 2022 outcome. EAG questions why D120SU DCO data not used for other outcomes as well?

Abbreviations: MPR, major pathologic response; ORR, overall response rate; CI, confidence intervals; OS, overall survival; D120SU, say 120 safety update

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.

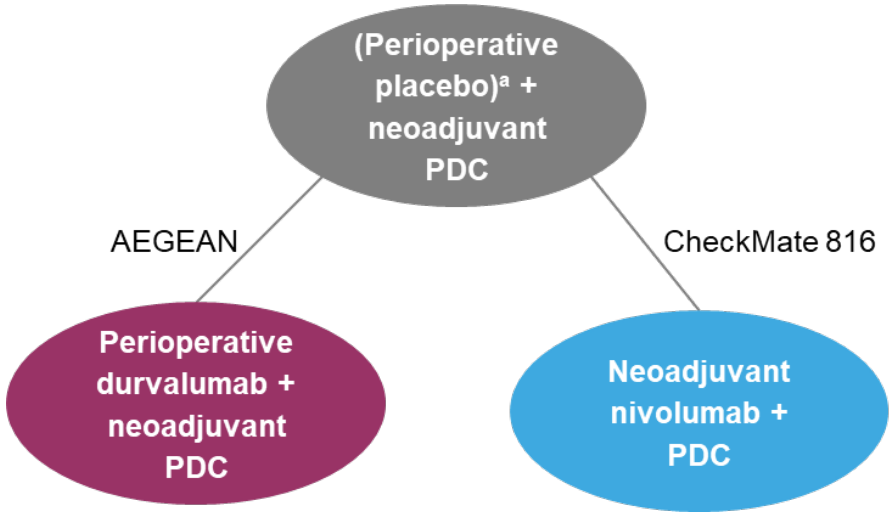
Population	NMA Analysis	Exclusions
mITT	Base-case	NA
mITT	Sensitivity analysis 1	Exclude studies with 2G chemotherapy
mITT	Sensitivity analysis 2*	Exclude studies with stage III patients only
mITT	Sensitivity analysis 3	Exclude Asia only studies
mITT	Sensitivity analysis 4	Exclude studies for any of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

Back to key issue

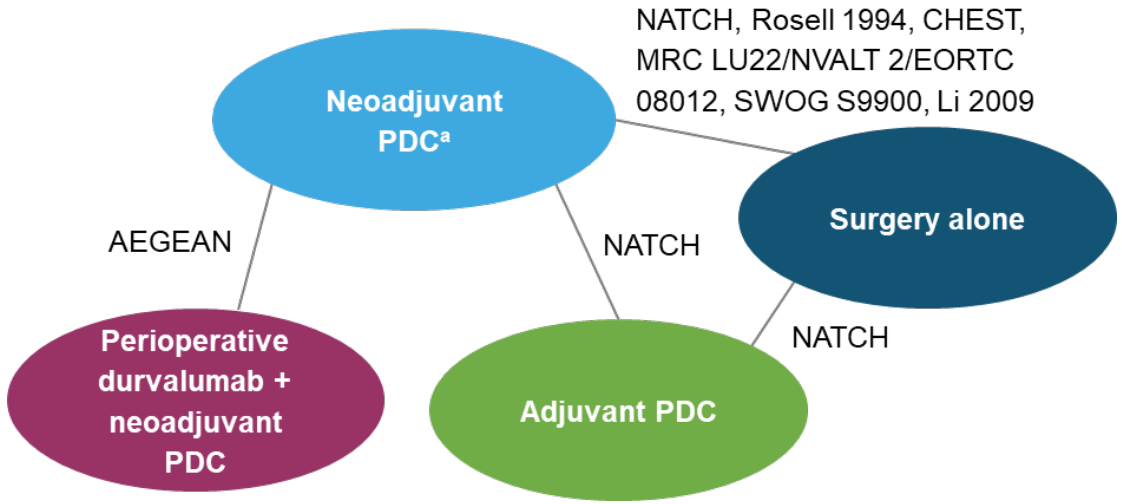
Abbreviations: NMA, network meta-analyses; MAIC, matching adjusted treatment analyses; ITC, indirect treatment comparison;

NMA/ITC network diagram(s)

Anchored MAIC



NMA



Back to key issue

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

NMA/ITC results

EFS hazard ratios (MAIC & NMA) versus neoadjuvant chemotherapy

Intervention/comparator	Source	HR 95%CI
Perioperative durvalumab	MAIC (base case) adjusted sample	[redacted]
Perioperative durvalumab	Unadjusted	[redacted]
Neoadjuvant nivolumab with chemotherapy	Checkmate 816	[redacted]
Adjuvant chemotherapy	NMA (sensitivity analysis 2)	[redacted]
Surgery alone	NMA (sensitivity analysis 2)	[redacted]

EFS hazard ratios (MAIC & NMA) perioperative durvalumab versus comparators

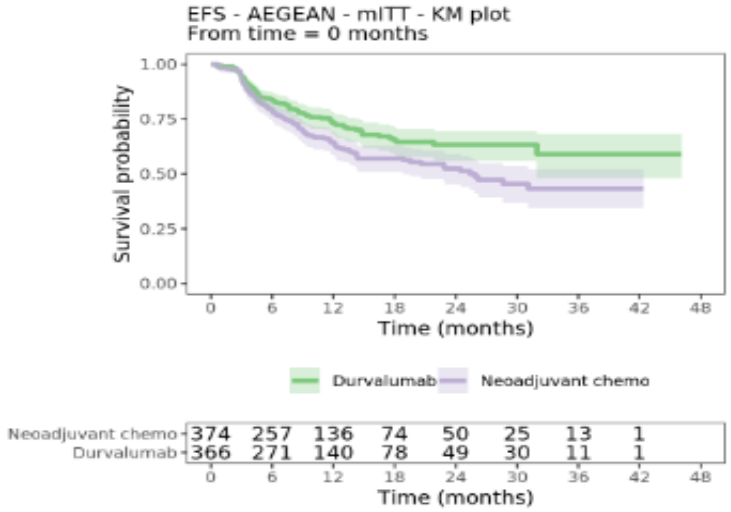
Comparator	Source	HR 95%CI
Neoadjuvant nivolumab with chemotherapy	Unadjusted comparison	[redacted]
Neoadjuvant nivolumab with chemotherapy	MAIC (base case)	[redacted]
Adjuvant chemotherapy	NMA (SA2, random effects)	[redacted]
Surgery alone	NMA (SA2, random effects)	[redacted]

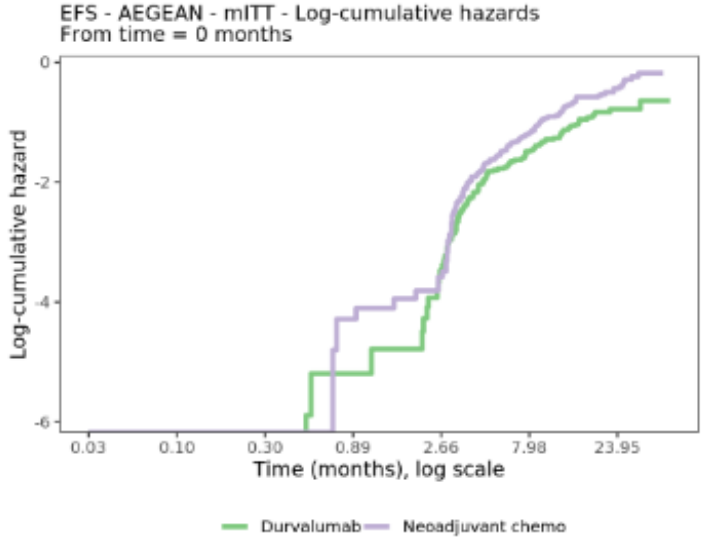
Back to key issue

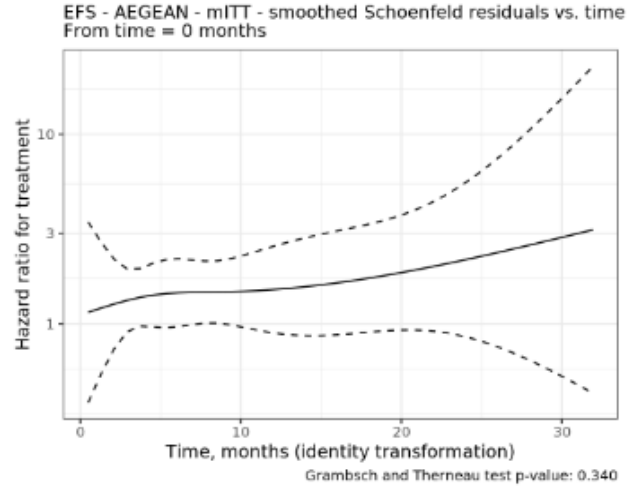
Abbreviations: MAIC, matching adjusted indirect comparison; NMA, network meta-analysis; EFS, event-free survival; HR, hazard ratio; CI, confidence intervals

Key Issue: Proportional hazards assumption

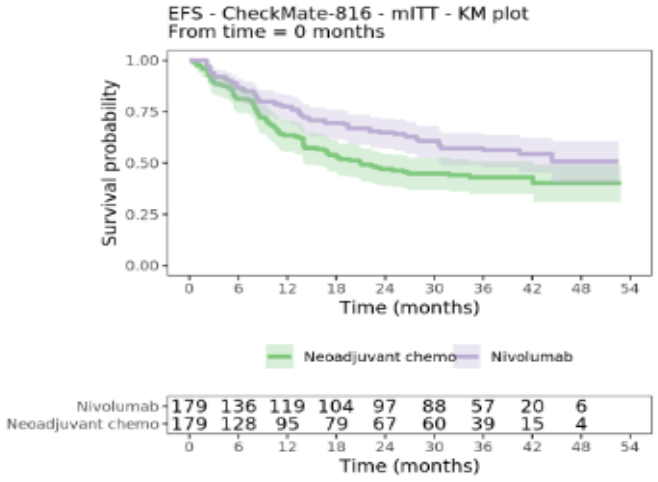
AEGEAN

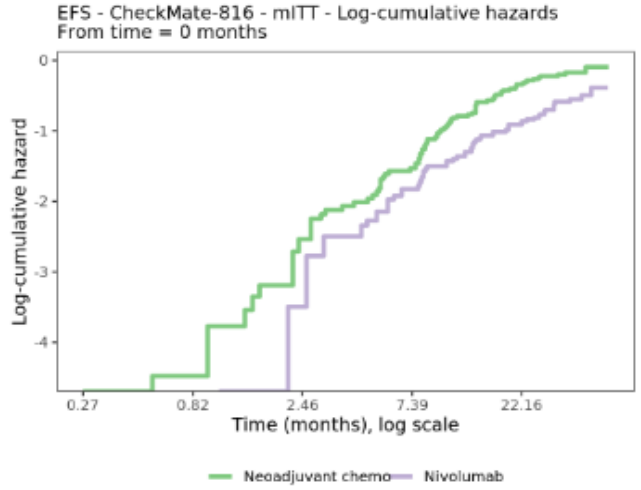


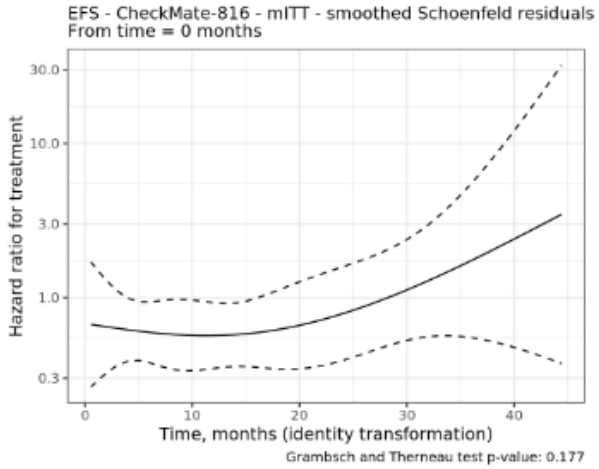




Checkmate-816







NICE Abbreviations: EFS, event free survival; KM, Kaplan-meier; mITT, modified intention to treat;

AEGEAN trial baseline characteristics

Characteristic	Groups	Durvalumab, n=366 (%)	Placebo, n (%)
Sex	Male	252 (68.9)	278 (74.3)
	Female	(31.1)	(25.7)
Smoking status	Current smoker	95 (26.0)	95 (25.4)
	Former smoker	220 (60.1)	223 (59.6)
	Never smoker	51 (13.9)	56 (15.0)
Stage	2	104 (28.4)	110 (29.4)
	3a	173 (47.3)	165 (44.1)
	3b	88 (24.0)	98 (26.2)
PD-L1 expression	<1%	122 (33.3)	125 (33.4)
	1-49%	135 (36.9)	142 (38.0)
	>=50%	109 (29.8)	107 (28.6)
Lymph node station	N0	110 (30.1)	102 (27.3)
	N1	75 (20.5)	87 (23.3)
	N2	181 (49.5)	185 (49.5)

NICE

Abbreviations: PD-L1, programmed cell death ligand 1; N0/1/2, number of nodes affected by NSCLC

*Only characteristics which EAG considered to be important effect modifiers for EFS and pCR (excluding geographic region) shown

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Included as per AEGEAN trial
Model reference curve	EFS reference curve was an extrapolation of the neoadjuvant CT EFS curve from AEGEAN, censored for death (lognormal distribution).
Intervention efficacy	EFS HR from durvalumab (MAIC population) compared to neoadjuvant CT applied to reference curve. Transitions assumed [redacted] LRR to DM based on clinical opinion
Comparator efficacy	Nivolumab: EFS HR vs neoadjuvant CT from CM-816 applied to reference curve Adjuvant CT and surgery alone: EFS HRs vs neoadjuvant CT from NMA applied
Utilities	Non treatment dependent utilities taken from AEGEAN, PACIFIC and KEYNOTE-189 trials for EF, LRR and DM1/2 health states respectively
Costs	NHS reference prices 2021/22, BNF 2023, eMIT and PSSRU
Resource use	Health state resource use extracted from SLR
Etc.	

Back to model overview

Abbreviations: BNF, British National Formulary; eMIT; electronic marketing information tool; PSSRU personal social services research unit; SLR, systematic literature review; EFS, event-free survival; MAIC, matching adjusted indirect comparison; CT, chemotherapy; LRR, locoregional recurrence; PSSRU, personal social services research unit

Comparison of cure with previous NSCLC appraisals (*for information only*)

Assumptions accepted by committee in previous appraisals:

- Substantial uncertainty linked to data immaturity (EFS/DFS)
- More formal modelling of cure would be preferable but limited by data availability
- Generally scenarios between 5 and 8 years with 90% plus cure proportions accepted for decision making

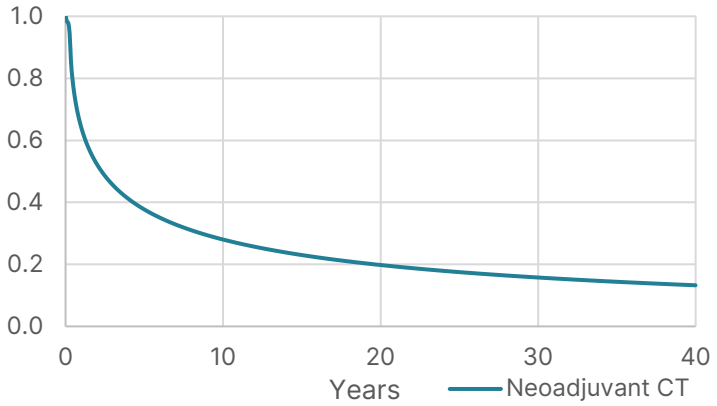
Assumption	Atezolizumab adjuvant maintenance (TA823)	Neoadjuvant nivolumab (TA876)	Adjuvant osimertinib (TA761)	Adjuvant osimertinib CDF exit (ID5120)
Cure point (CS)	5 years	5 to 7 years, linear reduction. (clinical opinion)	5 years (both interventions) Committee considered both	Warm up included (from 4 years)
Cure proportion	91.5%	0% (5 years) 95% (7 years)	95%	0% (4 years) 95% (5/8 years AM/Osi)
EAG position	Uncertainty around cure point and proportion. Offered alternative with 8 year cure point in both arms and one with 5 year for chemo and 6 or 7 years for atezo.	Consensus that cure occurs between 5-8 years but non on rates. Lack of evidence. Cure parameters explored through scenarios, little effect no ICER.	Would have preferred mixture-cure model. Proposed alternatives. Optimistic (5 years both) Pessimistic (5 year chemo, 8 year osimertinib)	EAG attempted MCM but data too immature for osimertinib.
Committee conclusion	Significant uncertainty. Considered both EAG approaches. (rec into CDF)	Committee concluded that the cure assumption applied was uncertain but explored sufficiently.	Significant uncertainty around cure. Considered both EAG approaches (rec into CDF)	Committee concluded MCM would have been preferable. Warm up should not be applied.

NICE Abbreviations: CS, company submission; CDF, cancer drugs fund; MCM, mixture cure model; ICER, incremental cost-effectiveness ratio; AM, active monitoring

Back to key issue

Company's model overview – Modelling efficacy at EFS

EFS to LRR and DM (TP1-2)

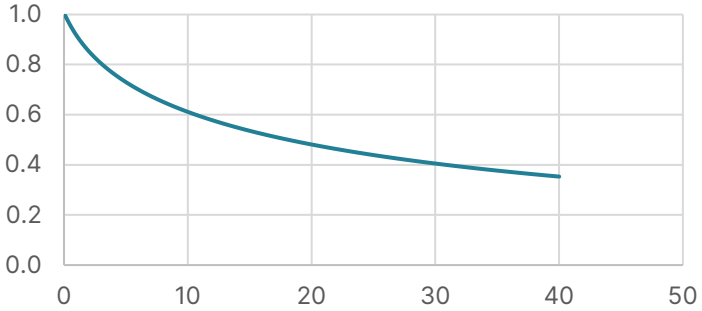


Piecewise neoadjuvant CT EFS reference curve, censored for death (3 months AEGEAN KM, then lognormal)

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

[redacted]

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

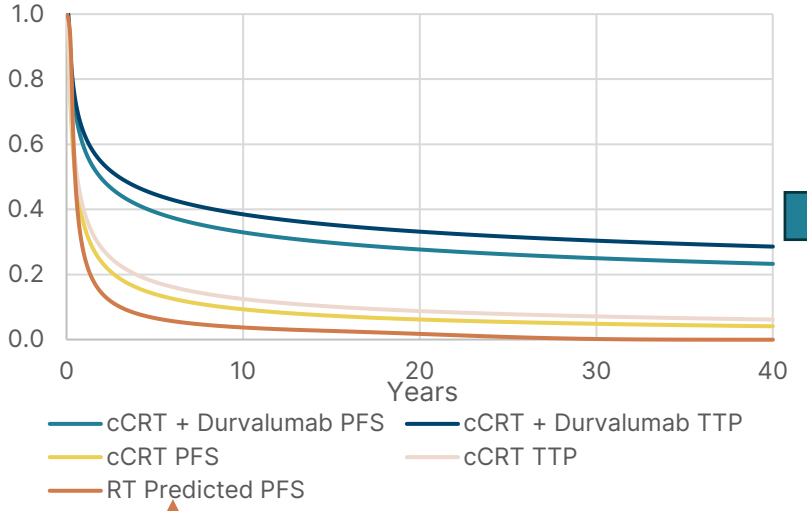
EFS to death modelled for each comparator

Back to model overview

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

Company's model overview – Modelling efficacy at LRR

Locoregional recurrence to DM (TP4) and Death (TP5a & 5b)



TPs for LRR to DM calculated from TTP

TPs for remaining in LRR calculated from PFS.

LRR to death (TP5a) is proportion not remaining LRR or moving to DM

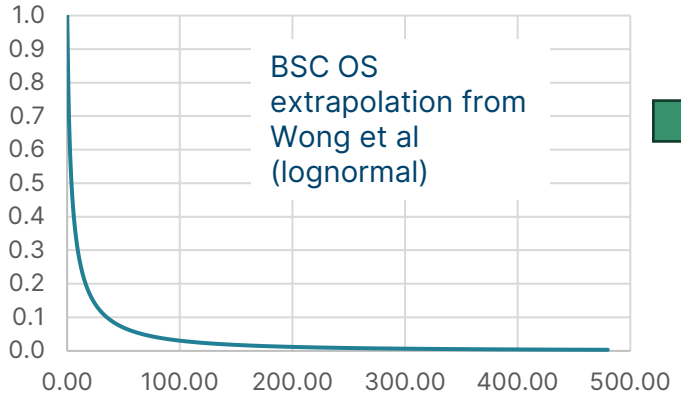
"Treatment type" weighted transition probabilities calculated

IO with no retreatment		Non-IO or IO with retreatment	
cCRT + Durvalumab	0%	cCRT + Durvalumab	46.6%
cCRT	82%	cCRT	43.8%
RT	18%	RT	9.6%

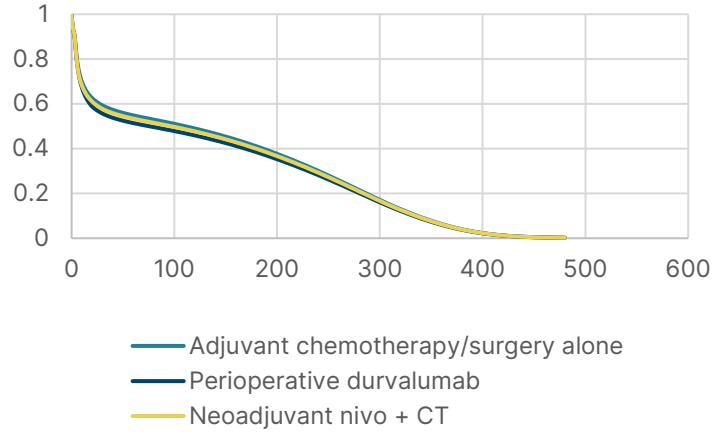
- RT PFS: Hung et al HR applied to cCRT curve
- Proportion of progression events assumed same as in PACIFIC

TP4 weighted transition probabilities (LRR to DM)

Locoregional recurrence to Death (TP5a & 5b)



20.5% weight



79.5% weight

TP5a weighted TPs per treatment E.g durvalumab: IO no retreatment TPs until month 21. Then IO retreatment TPs for eligible proportion.

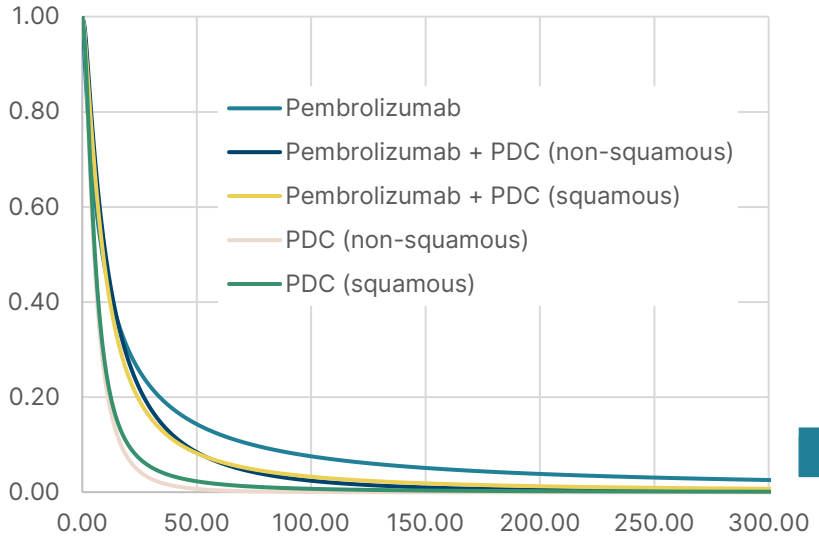
Back to model overview

NICE Abbreviations: EF, event free; LRR, loco-regional recurrence; DM, distant metastases; TP, transition probability; PSM, partitioned survival model

Company's model overview – Modelling efficacy at DM (1/2)

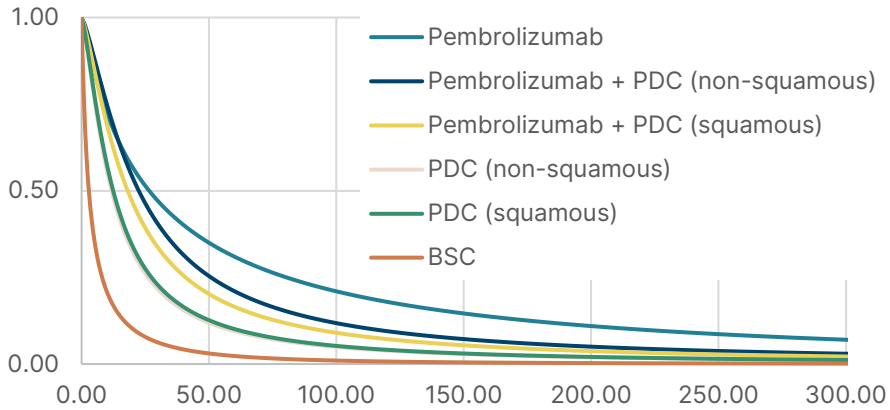
Distant metastases

PFS

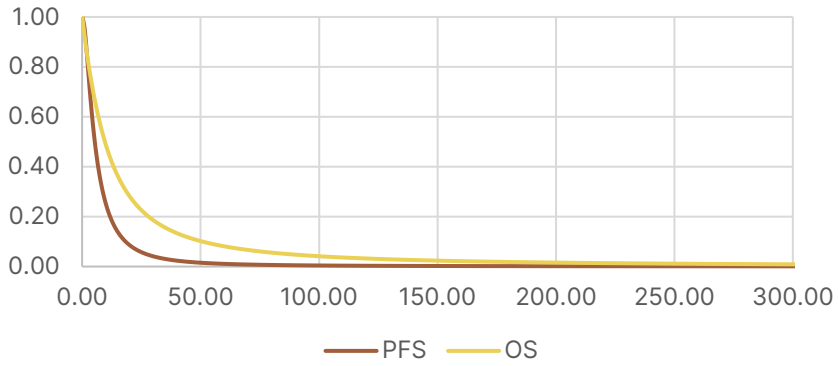


- PFS/OS extrapolated with distributions from original models
- BSC OS taken from Wong et al
- Atezolizumab assumed equivalent to pembrolizumab
- Market share used for weighted PFS and OS curves
- Nested PSMs created that can be used to model people in DM1 and DM2 and apply respective costs and QALYs

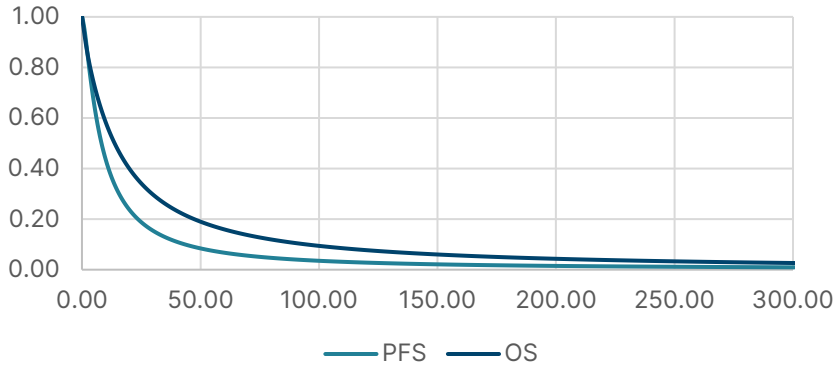
OS



Nested PSM for IO interventions with no retreatment



Nested PSM for IO interventions with retreatment or non IO interventions



Back to model overview

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

Company's model overview – Informing transition probabilities

Model structure

TP	Transition	Source
TP1 & TP2	EFS to LRR & EFS to DM	EFSs HRs from MAIC, CM-816 and NMA applied to neoadjuvant CT reference curve (censored for death). [redacted] of EFS events assumed to go to LRR, [redacted] to go to DM1. Note: First 3 months directly from AEGEAN, common to all interventions.
TP3	EFS to death	EFS to death curves from AEGEAN pooled and applied to all comparators
TP4	LRR to DM1	Weighted TTP survival curves of CRT with/without durvalumab (PACIFIC trial) and RT (Hung et al HR applied to CRT)
TP5	LRR to death	Weighted PFS curve of CRT with/without durvalumab (PACIFIC trial) and RT (Hung et al HR applied to CRT) minus equivalent weighted TTP survival curve. BSC (TP5b) only transitions to death (Wong et al survival curve)
TP6	DM1/2 to death	PFS and OS survival curves generated for 7 active comparators in DM1 and extrapolated. Weighted survival curve generated using market share estimates. (BSC only transitions to death)

NICE

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

Model outputs (CS base case)

 Abbreviations: CS, company submission