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

Technology appraisal committee D [07 August 2024]

For committee, contains Redacted information.

Chair: Megan John

Lead team: Carole Pitkeathley, Ben Searle, Rob Hodgson

External assessment group: Liverpool Research and Implementation Group (LRIG)

Technical team: Samuel Slayen, Adam Brooke, Jasdeep Hayre

Company: Merck Sharp and Dohme

Pembrolizumab as neoadjuvant (with chemotherapy) and adjuvant (as monotherapy) treatment for 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

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

Epidemiology

- 37,000 new cases of and 27,000 deaths from lung cancer in 2020
- 80% to 88% of lung cancer cases estimated to be NSCLC

Diagnosis and classification

- Often diagnosed at advanced/metastatic stage. NHS TLHC program aims to diagnose earlier
- Classified by histology, 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 fatigue, cough, chest pain
- Curative intent surgery often used for stage 1 to 3 NSCLC but recurrence is common
- 5-year survival is 68% (stage 1), 49% (stage 2), 25% (stage 3) and 9% (stage 4)

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

Patient perspectives

There is a chance of cure but recurrence is common and causes worry

Submission from Roy Castle Lung Cancer Foundation

- Relapse after surgery means that further potentially curative therapy is unlikely
- Note the significant EFS benefit of perioperative pembrolizumab from the KEYNOTE-671 trial
- It is important to patients that in administering neoadjuvant therapy the window for successful surgery is not missed (due to progression)
- Note that neoadjuvant nivolumab with chemotherapy was recommended in TA876 but there is still a need to explore additional therapies to improve outcomes and reduce recurrence

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

Abbreviations: EFS, event free survival

Clinical perspectives

Treatment aim is to cure more patients with resectable NSCLC

Submission from British Thoracic Oncology Group (BTOG)

- Increases in overall survival, event-free survival, pathological complete response and major pathological response would all be clinically significant
- Resectable NSCLC is currently treated with 3 cycles of neoadjuvant nivolumab with chemotherapy (TA876) – For Stage 2A to 3B disease
- An area of concern is that patients with unresectable NSCLC may be pushed towards this pathway instead of radical concurrent chemoradiotherapy
- Expect perioperative pembrolizumab to improve overall survival compared to neoadjuvant nivolumab
- There is evidence that the adjuvant component might especially improve outcomes in the non-pCR patients over just the neoadjuvant component

"The pathway is well defined on paper but in clinical practice there is wide variation"

"I do feel a few months of neoadjuvant therapy does make planning surgery much easier for surgical departments"

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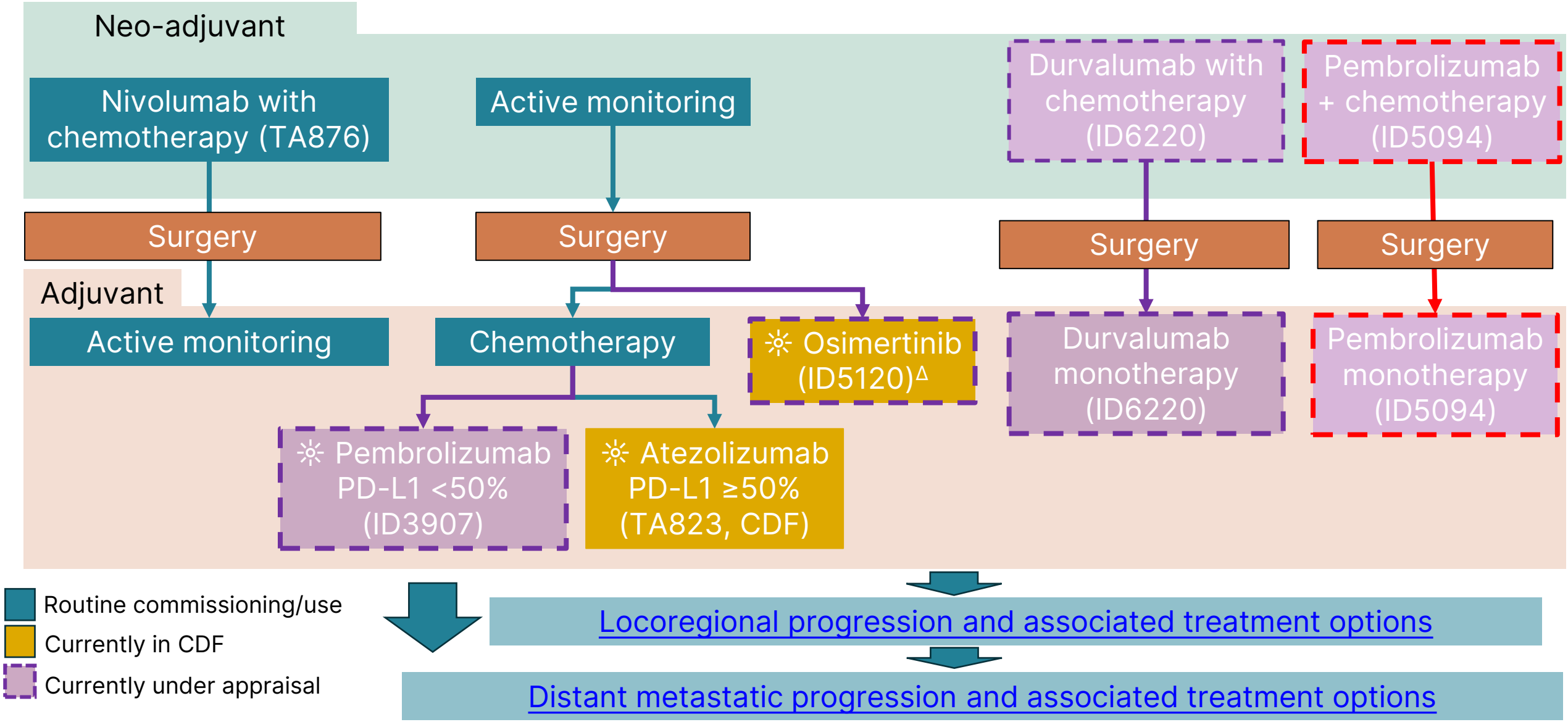
Abbreviations: pCR, pathologic complete response (absence of viable tumour cells in tissue and lymph node samples taken at surgery); EFS, event-free survival (absence of an event that precludes surgery, recurrence after surgery or death). mPR (viable tumour cells 10% or less of samples taken)

Equality considerations

No equalities issues were raised during the course of this appraisal

Treatment pathway (resectable NSCLC)



NICE Abbreviations: CDF, cancer drugs fund

ΔEGFR mutation positive disease only, CDF exit appraisal ongoing ☼ adjuvant treatments only used after complete resection (R0)

Technology (Keytruda, MSD)

Marketing authorisation	• "Pembrolizumab (KEYTRUDA ®) in combination with platinum-containing chemotherapy as neoadjuvant treatment, then continued as a monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung cancer (NSCLC) at high risk of recurrence in adults" • Licence granted
Mechanism of action	• Pembrolizumab is a checkpoint inhibitor targeting and blocking PD-1 which is responsible for dampening T-lymphocyte immune responses in the tumour microenvironment • It is combined with chemotherapy as a neo-adjuvant treatment and used as monotherapy as an adjuvant treatment
Administration	• Neoadjuvant: 200mg in combination with platinum chemotherapy, every 3 weeks for four cycles • Adjuvant as monotherapy • 200mg every 3 weeks up to 13 cycles or • 400mg every 6 weeks up to 6 cycles (with 200mg loading dose for first cycle)
Price	• £2,630 per 100mg vial • Pembrolizumab has a commercial access agreement

Key issues

Issue	Resolved?	ICER impact
Comparators	No	Unknown
Generalisability of KEYNOTE-671 trial to NHS clinical practice	No	Unknown
Limited comparative clinical effectiveness evidence	No	Unknown
Limitations of time varying EFS hazard-ratio NMAs	No	Large
Longer term company estimates of relative effectiveness of perioperative pembrolizumab	No	Large
Potential underestimation of mortality for those considered “cured” at 5 years	No	Small

Abbreviations: EFS, event-free survival; ICER, incremental cost-effectiveness ratio

Key issues: Comparators

Background

- Company did not provide evidence for four of the comparators listed on the final scope (nCRT, atezolizumab [TA823] maintenance, osimertinib [TA761/ID5120] and perioperative durvalumab [ID6220])

Company

- nCRT has a weak recommendation in NG122 and is only for Stage 3A (N2) disease. Atezolizumab still in CDF.
- Adjuvant chemotherapy and osimertinib decisions are distinct from this appraisal (only R0 patients). In TA876 nivolumab had lower ICER compared to adjuvant chemotherapy than surgery alone (minimises risk)
- Unclear if company has access to latest data from AEGEAN (durvalumab trial).
- EFS HR in AEGEAN and Checkmate-816 are similar. Durvalumab's omission does not pose large decision risk.

EAG comments

- Clinical expert considers nCRT to be largely displaced by neoadjuvant nivolumab with chemotherapy
- NICE should clarify whether comparators which may be recommended shortly before a technology's appraisal committee meeting should be included in the CS as relevant comparators

Other considerations (*for information*)

- Adjuvant osimertinib (ID5120) and perioperative durvalumab (ID6220) appraisals ongoing after ACM1
- ID6220, CDF clinical lead considered neoadjuvant nivolumab was only relevant comparator. Committee concluded it was the most relevant.

Are the comparators modelled appropriate?

Abbreviations: nCRT, neoadjuvant chemoradiotherapy; N2, two lymph node involvement; CDF, cancer drugs fund; R0, complete resection (clear margins); ICER, incremental cost-effectiveness ratio; EFS, event free survival; ACM, appraisal committee meeting

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Key definitions

- Event free survival (EFS) – An event that precludes surgery (including progression), a progression event after surgery or death
- Disease free survival (DFS) – An event of progression or death after surgery. Specific to people with complete resection and used in adjuvant appraisals.
- Pathologic complete response (pCR) – the absence of viable tumour cells in tissue and lymph node samples taken at surgery

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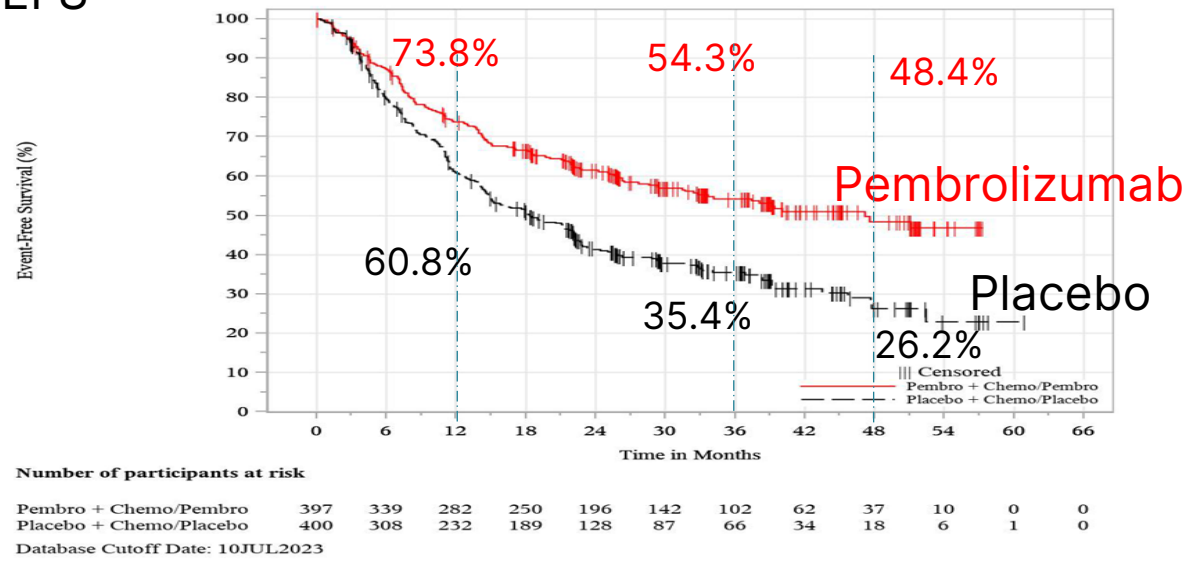
Clinical trial results (KEYNOTE-671)

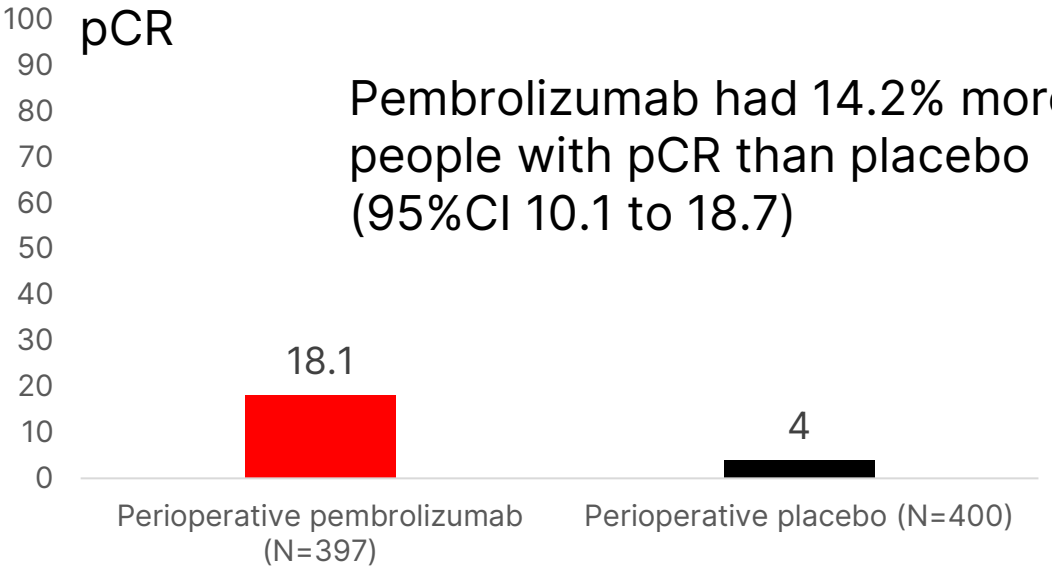
EFS



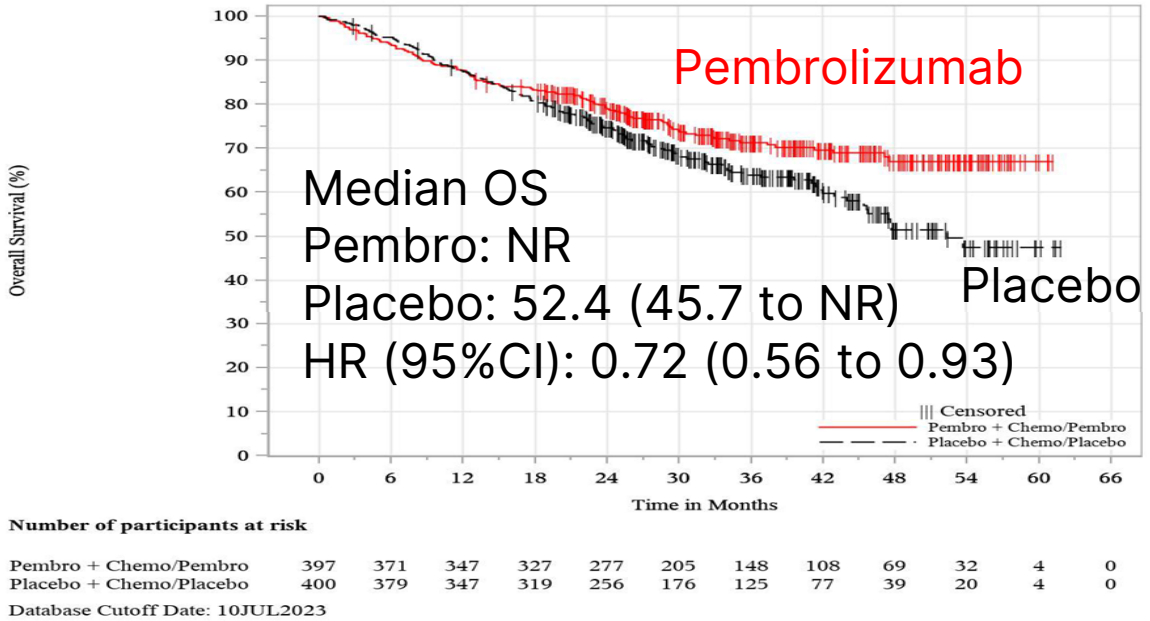
Median follow up: 29.8 months

Intervention	Events/patients (%)	Median EFS (95%CI)
Perioperative pembrolizumab	174 (43.8)	47.2 (32.9 to NR)
Perioperative placebo	248 (62.0)	18.3 (14.8 to 22.1)
HR (95% CI)		0.59 (0.48 to 0.72)

pCR



OS



Abbreviations: EFS, event-free survival; pCR, pathologic complete response; OS, overall survival; CI confidence intervals; NR, not reached; HR, hazard ratio

Results by pCR status

Results by subgroup

Key issues: Generalisability

Background

- Mean age in trial was 63.1 years compared to estimated mean age of 70 years in NHS practice. Immunotherapy may be less suitable as people get older. Starting age has substantial effect on QALYs due to cure assumption
- In the clinical trial the adjuvant component (pembrolizumab monotherapy) was given to all, regardless of pCR.

Company

- Clinical advice is that people with pCR would not be offered adjuvant component in NHS (overtreatment concerns)
- Submitted scenarios to explore removing costs of adjuvant pembrolizumab from people in the model with pCR (pCR stopping rule scenarios)

EAG comments

- Mismatch between adjuvant pembrolizumab for those with pCR in trial and not in practice is generalisability issue.
- KEYNOTE-671 data does not allow separation of the effectiveness of the neoadjuvant and adjuvant components of perioperative pembrolizumab. Scenarios submitted by company are of limited value for decision making.

Other considerations (*for information*)

- BTOG expert submission: the adjuvant component may be especially useful in people without pCR.
- Committees in ID6220 (perioperative durvalumab) and ID5120 (adjuvant osimertinib, EGFR+ NSCLC) concluded the starting age of the model should be set to 70 years to reflect NHS practice

Is the data from KEYNOTE-671 generalisable to NHS clinical practice? What is the age of patients having surgery for NSCLC in NHS practice?

EFS results by pCR subgroup

Abbreviations: pCR, pathologic complete response;

Key issues: Limited comparative clinical effectiveness evidence

Background

- Only indirect evidence available and only for outcome of EFS. No comparison of pCR, mPR, AEs or HRQoL.
- OS data from the KEYNOTE-671 trial was too immature for the company to generate reliable ITC results.

Company

- pCR, adverse events and HRQoL would not directly inform the cost-effectiveness analyses. pCR is a surrogate outcome predictive of EFS and OS which are relatively mature in KEYNOTE-671
- Feasibility assessment for HRQoL and AE NMAs they would not be possible due to data availability issues (e.g differences in way these outcomes were reported in various identified trials)

EAG comments

- Clinical advice agrees that EFS is an appropriate outcome in the perioperative setting
- Conclusions cannot be drawn about the relative effectiveness of perioperative pembrolizumab on OS, clinical expert opinion should inform assessment of long-term effectiveness.

Other considerations

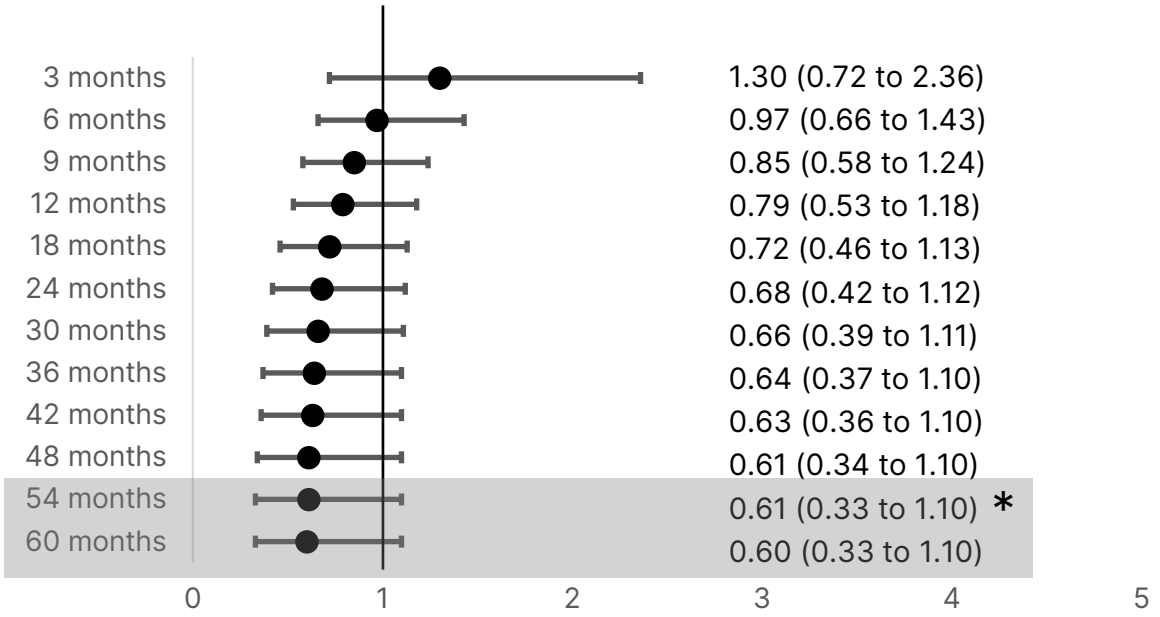
- BTOG submission: EFS is already recognised as a surrogate for overall survival

Are the outcomes reported and compared suitable for decision making?

Abbreviations: pCR, pathologic complete response; mPR, major pathological response; HRQoL, health related quality of life; ITC, indirect treatment comparison; EFS, event-free survival; OS, overall survival; AE, adverse events

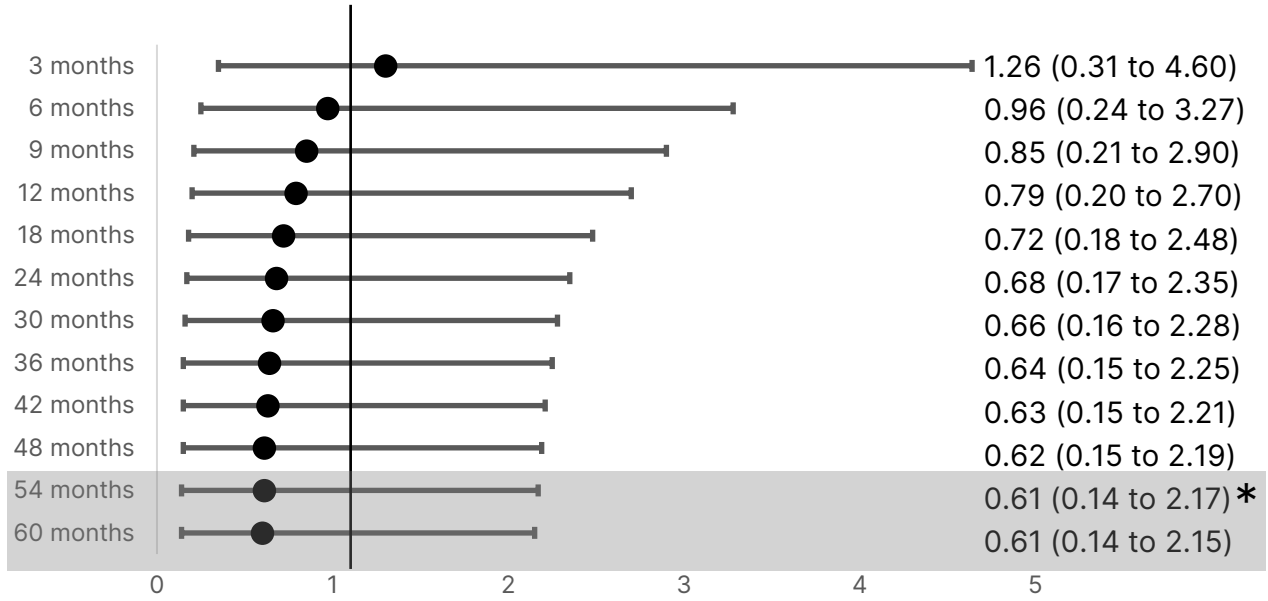
NMA results summary (comparison versus nivolumab)

Time-varying fixed effects



Time constant NMA	Hazard Ratio (95% CrI)
Fixed effects	0.87 (0.59 to 1.27)
Random effects	0.87 (0.10 to 7.27)

Time-varying random effects



In the model

Company base case: time-varying, fixed effects

EAG base case: time-constant, fixed effects

For reference

KEYNOTE-671 HR versus neoadjuvant chemotherapy: 0.59 (0.48 to 0.72) – Median follow up 29.8 months

CheckMate-816 HR versus neoadjuvant chemotherapy: 0.65** (0.47 to 0.90) – Median follow up 29.5 months

NMA methods | NMA diagram | More NMA results

Abbreviations: CrI, credible interval; HR, hazard-ratio; NMA, network meta-analysis. *Shaded grey boxes are based on model extrapolations and not observed data. **CheckMate-816 HR presented is adjusted for adjuvant therapy, unadjusted HR is 0.63

Key issues: Time-varying versus constant hazard-ratios

Background

- Company did time-constant and time-varying NMAs to compare perioperative pembrolizumab to comparators.

Company

- Standard statistical tests held, and PH assumption not violated but can only detect most pronounced PH violations
- Standard in oncology submissions to model within-trial curves independently (implies non-proportional hazards)
- HR for perioperative pembrolizumab decreases while HR for neoadjuvant nivolumab increases over time
- Biologically plausible for HRs to vary across network of evidence (differences in timing of surgery, addition of adjuvant immunotherapy component) so time-varying HRs more appropriate and used in base case (fixed effects)

EAG comments

- Clinical advice is that the long-term biological plausibility of time-varying HRs is uncertain
- No sufficiently strong rationale provided to support using time-varying NMA over time-constant NMA results
- Concern that width of 95% CrIs of time-varying HRs do not change or reflect the number of patients informing each time point. Time-varying NMA does not provide robust evidence to support EFS HRs changing over time.
- PH violation tests for KEYNOTE-671 and CheckMate-816 trials not met, appropriate to conduct time-constant NMAs and these results can be used to inform the model (and fixed effects versions are used in EAG base case)

Are the results of the time-constant or time-varying NMA more appropriate to inform the economic model?

Abbreviations: NMA, network meta-analysis; PH, proportional hazards; HR, hazard-ratio; CrI, credible interval; EFS, event-free survival;

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

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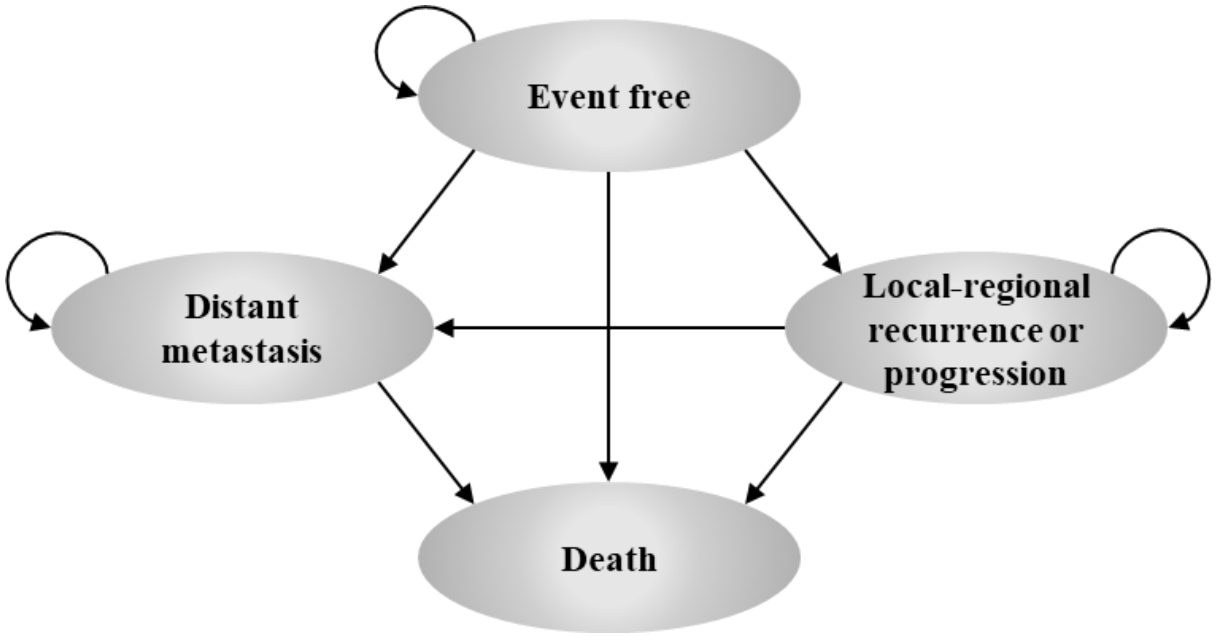
Company's model overview

Model structure



- Technology affects **costs** by:
  - Acquisition costs of perioperative treatment
  - Differential health state resource and treatment costs
- Technology affects **QALYs** by:
  - Health state occupancy and utilities accrued in each health state
  - Adverse events
- Assumptions with greatest ICER effect:
  - Time-constant EFS HR over time varying
  - Assuming EFS treatment effect waning after observed trial period (and before cure)

Evidence informing the model

Modelling of EFS

Modelling of LR/P

Modelling of DM

- Health states after EFS have very similar results between arms (differ only due to IO retreatment)
- The majority of the QALYs are accrued in the EFS health state (especially due to the cure assumption)
- Anything that drives differences in EFS is therefore a key driver of the results

Abbreviations: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; EFS, event free survival; LR/P locoregional recurrence or progression; DM, distant metastases; HR, hazard ratio

Key issues: Extrapolation of longer-term relative efficacy (EFS)

Background

- Company base-case: time-varying HRs applied to 62 months (maximum KEYNOTE-671 follow up) after which the final hazard-ratio is carried forward for the lifetime of the model.

Company

- No explicit modelling of treatment effect waning in base case. If modelled, gradually trending HRs to 1 over time would be in line with approaches to treatment effect waning in previous NICE appraisals of immunotherapies
- In metastatic setting, NICE appraisals have assumed effect waning around 3-5 years after treatment stopping
- Included scenarios in submission which present time-varying HRs versus pembrolizumab trending to 1 between 5 and 7 years. (60 and 84 months respectively)

EAG comments

- No evidence for sustained EFS effect of perioperative pembrolizumab beyond trial follow up. Carrying HR forward from last observed point might overestimate pembrolizumab's effectiveness (particularly with time varying HRs)
- Preferable to apply HR of 1 to pembrolizumab EFS curve beyond observed data (41.1 months for nivolumab and 62 months for surgery alone) with time-constant hazard-ratios applied before this point.
- Both time-trending and instantaneous modelling of treatment effect waning plausible and should be considered.

How should the longer-term relative effects of perioperative pembrolizumab on EFS be modelled?

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

Key issues: Modelling of cure

Background

- 95% of people in EFS at 7 years will have no further risk of progression and general population mortality. Cure proportion increases linearly from 0% at 5 years to 95% at 7 years to prevent visible kink in EFS curve

Company

- Cure portion and time points informed by clinical opinion that noted most relapses occur within 5 years of surgery and in line with TA761 (EGFR+ NSCLC) and TA876. Gradual cure period used to prevent visual kink in EFS curve
- A narrower cure period with 100% cure portion also plausible and included in scenario (100% at 7 year)

EAG comments

- Clinical opinion agrees risk of recurrence very low beyond 5 years. Further NSCLC likely to be treated as new primary cancer. Considers cure point and portion broadly appropriate. Cure scenarios had limited effect on results.
- However, notes evidence (Janssen-Heijnen study*) that mortality beyond 5 years might be higher than general population.
- Included a modifier (1.453) in base case to reflect somewhat higher mortality in the "cured" population. (5 year survival by age group and stage weighted by proportions in KEYNOTE-671 study to derive modifier)

Is the company modelling of cure appropriate?
How should mortality be modelled for the cured population?

Precedent for modelling of cure

Abbreviations: EFS, event-free survival; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; ICER, incremental cost-effectiveness ratios

*Janssen-Heijnen ML, van Steenbergen LN, Steyerberg E, Visser O, De Ruysscher DK, Groen HJ. Long-term excess mortality for survivors of non-small cell lung cancer in the Netherlands. J Thorac Oncol. 2012; 7:496-502.

Health state utility values

- Utility value in the EF state was higher than age and sex matched general population estimate
- EAG submitted scenario with general population utility value at EF

Appraisal	EF	LR/P	DM (PF)	DM (PD)
ID5094	0.882**	0.776	0.727	0.657 (NS) 0.679 (S)
ID5094 (EAG scenario)	0.822	0.776	0.727	0.657 (NS) 0.679 (S)
ID6220*	0.829	*Redacted*	*Redacted*	*Redacted*
TA823	0.80	0.77	0.71	0.69

- *In ID6220 committee accepted a general population utility estimate for the EF state (0.829) and also an EAG adjustment whereby a 0.2 decrement was applied to the EF state value to generate the LR/P utility value and DM health state values were adjusted down to maintain the original decrement
- Reducing the utility value in the EF state benefits neoadjuvant nivolumab, reducing it in the subsequent health states benefits perioperative pembrolizumab however selection of utility values has a relatively limited effect on the ICERs overall.

Which utility values should be used in the model for decision making?

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Abbreviations: EF, event-free; LR/P, loco-regional progression or recurrence; DM (PF), distant metastases-progression free; DM (PF), distant metastases-progressed disease
** Utility estimate without AEs

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Cure	95% cured at 7 years (linearly from 0% at 5 years) have no risk of progression and general population mortality.	As per company base case however with higher mortality than general population (application of 1.453 modifier)
EFS HR	Time-varying (fixed effects) hazard-ratios until 62 months (latest KEYNOTE-671 data cut).	Time-constant hazard-ratio applied until 41.2 months (nivolumab) and 62 months (surgery alone)
Treatment effect waning	Final time-varying hazard ratio used for remainder of model time horizon	Assumed HR of pembrolizumab to comparators rises to 1 from the above timepoints.

Additional scenarios (EAG and company)

Parameter	Base case	Scenario/s
EFS HR	See above.	No difference in EFS between pembrolizumab and nivolumab (EAG)
Utility	Utility in EFS state higher than general population	EFS utility limited to age/sex matched general population utility (EAG)
Cure	5-7 year cure period, linear increase to 95%	Base case with 100% cure proportion Cure periods of 3-5, 5-10 and 7-10 years. (company)

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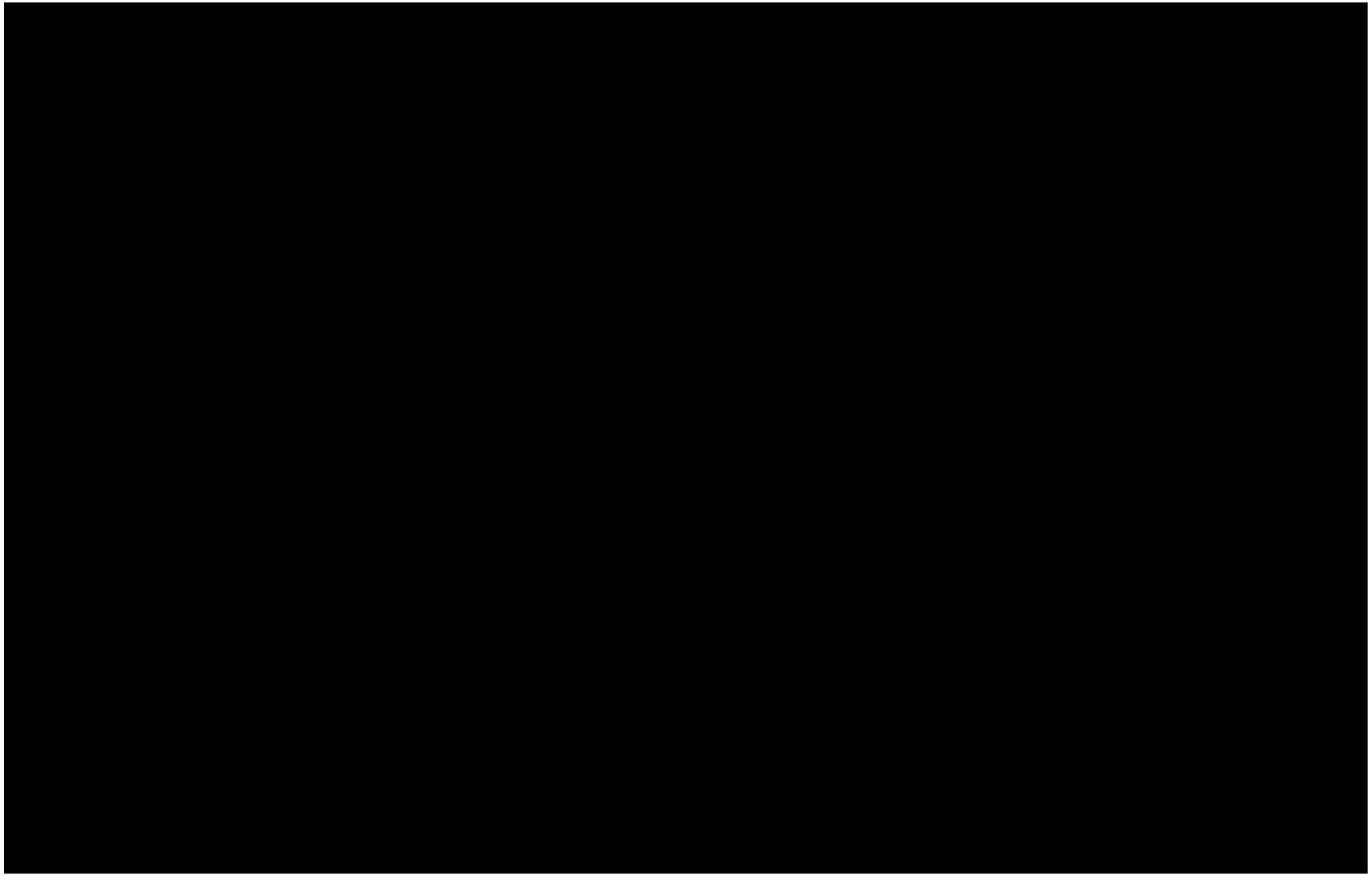
Abbreviations: HR, hazard ratio; EFS, event-free survival

Effects of assumptions on EFS



6. EAG base case

This redacted graph shows the effect of different assumptions on the EFS health state traces for perioperative pembrolizumab and neoadjuvant nivolumab.

Abbreviations: EFS, event-free survival; TEW, treatment effect waning; TC-HR, time-constant hazard ratio; SMR, standardised mortality ratio

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Severity modifier

Company did not make a case for application of severity modifier

- MSD considers that pembrolizumab does not qualify for a severity modifier in this indication as the expected QALY loss for standard of care versus the general population does not meet any severity modifier threshold.

Abbreviations: MSD, Merck, Sharp and Dohme

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**.
- MSD consider that pembrolizumab should be considered for baseline commissioning however remains committed to patient access and are willing to discuss managed access if necessary
- When are subsequent data-cuts expected from KEYNOTE-671 and what will be reported?

Abbreviations: MSD, Merck, Sharp and Dohme

Cost-effectiveness results

- Cost effectiveness results cannot be reported here due to presence of confidential discounts for included technologies
- The company base case ICER is below £20,000 per QALY gained
- The EAG base case ICER is above £30,000 per QALY gained
- All results are presented in Part 2 slides for committee consideration

Abbreviations: ICER, incremental cost effectiveness ratio

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

Supplementary appendix

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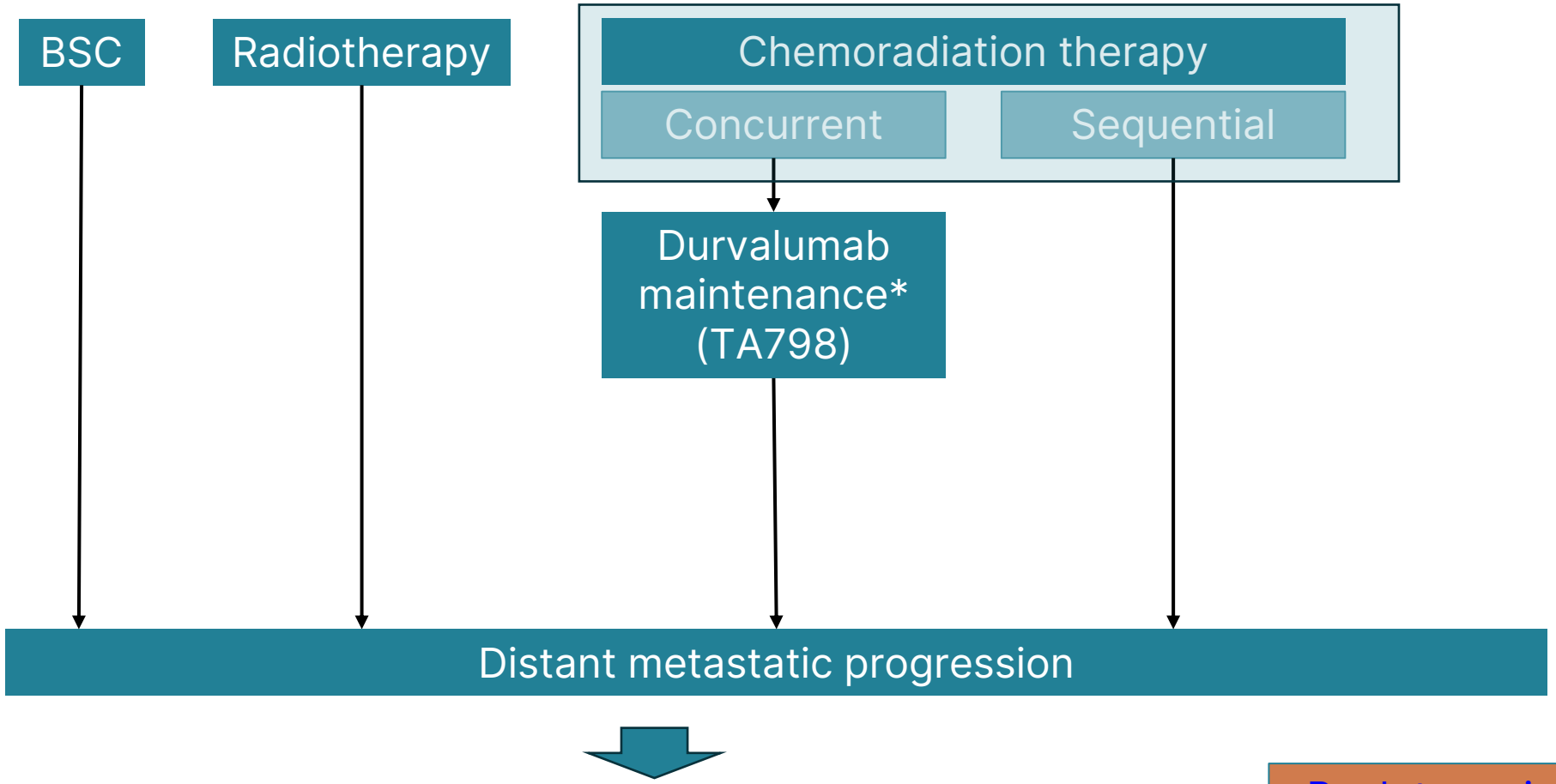
Treatment pathway

Unresectable locally advanced



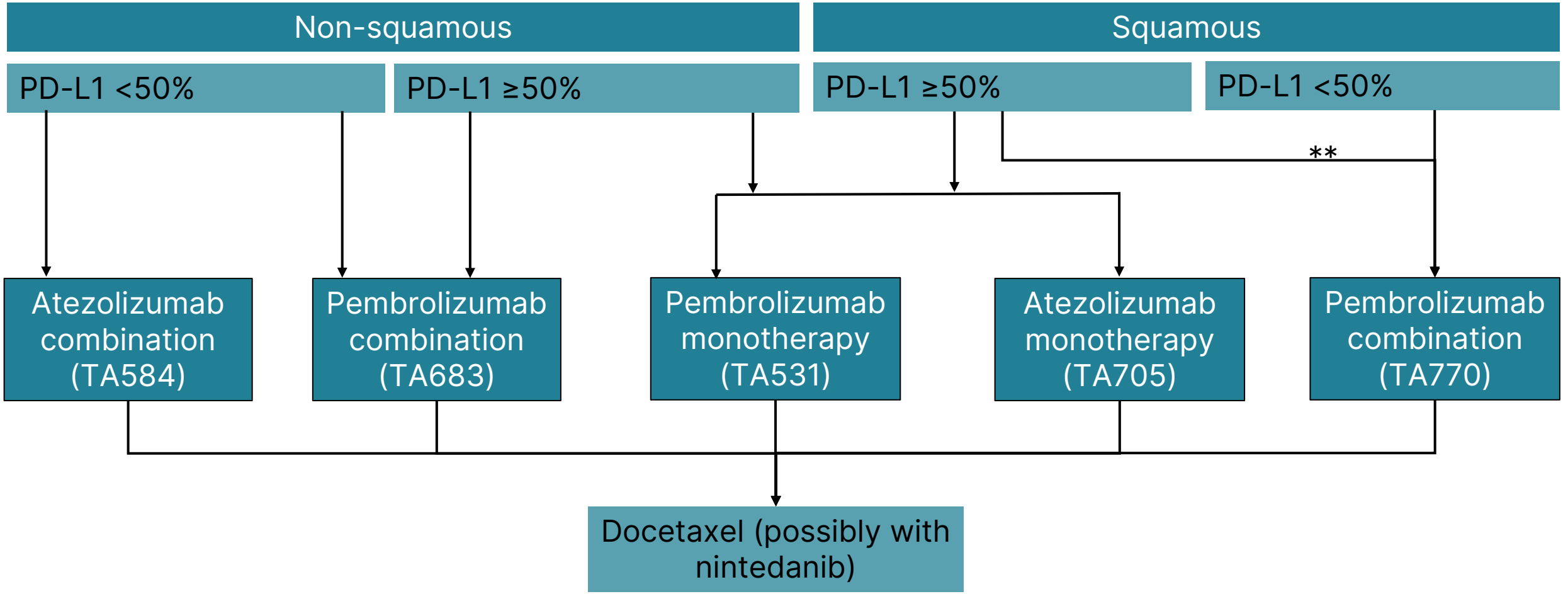
Back to main treatment pathway

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

Clinical trial results ii – EFS by pCR subgroup

Perioperative pembro vs perioperative placebo
Keynote-671

Neoadjuvant nivolumab vs neoadjuvant chemo
Checkmate-816

[redacted]

Back to results

Back to generalisability

NICE Abbreviations: EFS, event-free survival; pCR, pathologic complete response; CI confidence intervals

Clinical trial results (EFS subgroup analyses)

Subgroup	Hazard ratio (95% CI)
PD-L1 50% or over	0.48 (0.33 to 0.71)
PD-L1 50% or under	0.63 (0.51 to 0.79)
PD-L1 positive (1% or over)	0.51 (0.39 to 0.66)
PD-L1 negative (under 1%)	0.75 (0.56 to 1.01)
PD-L1 50% or over	0.48 (0.33 to 0.71)
PD-L1 1 to 49%	0.52 (0.36 to 0.73)
PD-L1 under 1%	0.75 (0.56 to 1.01)
Stage 2 disease	0.59 (0.40 to 0.88)
Stage 3 disease	0.58 (0.46 to 0.72)
EGFR mutation positive	0.32 (0.11 to 0.91)
EGFR mutation negative	0.55 (0.38 to 0.81)
EGFR status unknown/missing	0.62 (0.49 to 0.79)
No ALK translocation status	0.50 (0.35 to 0.73)
ALK translocation status missing	0.62 (0.49 to 0.78)

EFS results for subgroups on scope where data was reported in submission.

Back to results

Abbreviations: PD-L1, programmed cell death ligand 1; HR, hazard ratio; CI, confidence interval; ECOG; Eastern cooperative oncology group performance scale; TPS, tumour proportion score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase

Adverse events

Rates are similar in the pembrolizumab and placebo arms of KEYNOTE-671

	Pembrolizumab (n=396)		Placebo (n=399)	
	n	%	n	%
One or more AE	394	99.5	394	98.7
No AE	2	0.5	5	1.3
Drug-related AE	383	96.7	381	95.5
Grade 3-5 AE	257	64.9	213	53.4
Grade 3-5 drug-related AE	179	45.2	151	37.8
Serious AE	165	41.7	133	33.3
Serious drug-related AE	73	18.4	58	14.5
Death	26	6.6	15	3.8
Death due to a drug-related AE	4	1.0	3	0.8
Discontinued any drug due to an AE	102	25.8	70	17.5

AEs more frequently reported in the pembrolizumab arm than the placebo arm were hypothyroidism (10.9% versus 1.5%), rash (17.4% versus 8.5%), fatigue (31.6% versus 25.3%), insomnia (12.9% versus 6.5%), dyspnoea (18.4% versus 13.0%), alanine aminotransferase increase (14.9% versus 10.3%), pruritus (13.4% versus 8.8%), pyrexia (12.6% versus 8.0%), and peripheral oedema (10.1% versus 6.0%).

NICE Abbreviations: AE, adverse event

NMA methodology

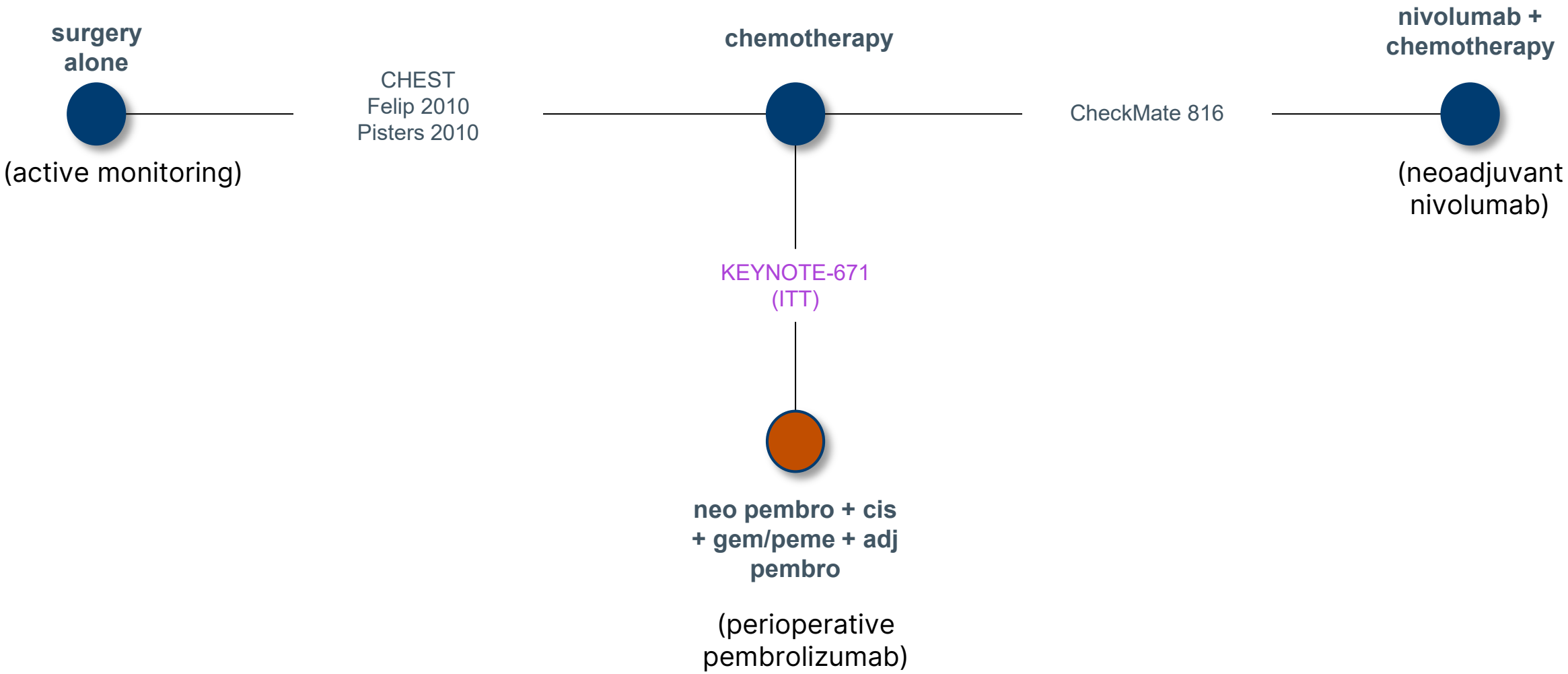
- Fixed and random effects NMAs with both time-constant and time-varying EFS HRs conducted. Company prefer fixed effects because main link informed by 2 large well-designed studies (KEYNOTE-671 and CheckMate-816)
- Company preferred the time-varying NMAs because they consider non-proportional hazards between included trials to be more plausible (noting that the tests which failed to detect PH violations are not very sensitive
- Also note that HR for [redacted]
- Company consider that non-proportional hazards biologically plausible as pembrolizumab has later surgery than nivolumab and added adjuvant component (presumed to eliminate post-surgery micro-metastases)
- Company base case informed by fixed-effects time-varying NMAs. But all results presented and scenarios available for fixed-effects and time-constant HRs

Back to NMA results

Back to NMA issue

Abbreviations: NMA, network meta-analysis; EFS, event-free survival; HR, hazard ratio; PH, proportional hazard;

NMA network diagram - EFS



Back to NMA issue

Abbreviations: NMA, network meta-analysis; ITT, intention to treat

NMA results summary (versus both comparators)

Analysis	HR (95% CrI)	
	Versus surgery alone	Versus neoadjuvant nivolumab
Time-varying		
Fixed effects	3 months: 0.49 (0.33 to 0.71) 12 months: 0.48 (0.37 to 0.63) 48 months: 0.48 (0.32 to 0.70)	3 months 1.30 (0.72 to 2.36) 12 months: 0.79 (0.53 to 1.18) 48 months: 0.61 (0.34 to 1.10)
Random effects	3 months: 0.47 (0.14 to 1.39) 12 months: 0.48 (0.14 to 1.37) 48 months: 0.48 (0.14 to 1.38)	3 months: 1.26 (0.31 to 4.60) 12 months: 0.79 (0.20 to 2.70) 48 months: 0.62 (0.15 to 2.19)
Time constant		
Fixed effects	0.52 (0.41 to 0.65)	0.87 (0.59 to 1.27)
Random effects	0.49 (0.09 to 2.56)	0.87 (0.10 to 7.27)

Back to NMA results

Back to NMA issue

Abbreviations: NMA, network meta-analysis; HR, hazard ratio; CrI, credible interval
Selected time points only, full results can be seen in Tables 22 to 26 of the Company submission document B

Key Issue: Proportional hazards assumption

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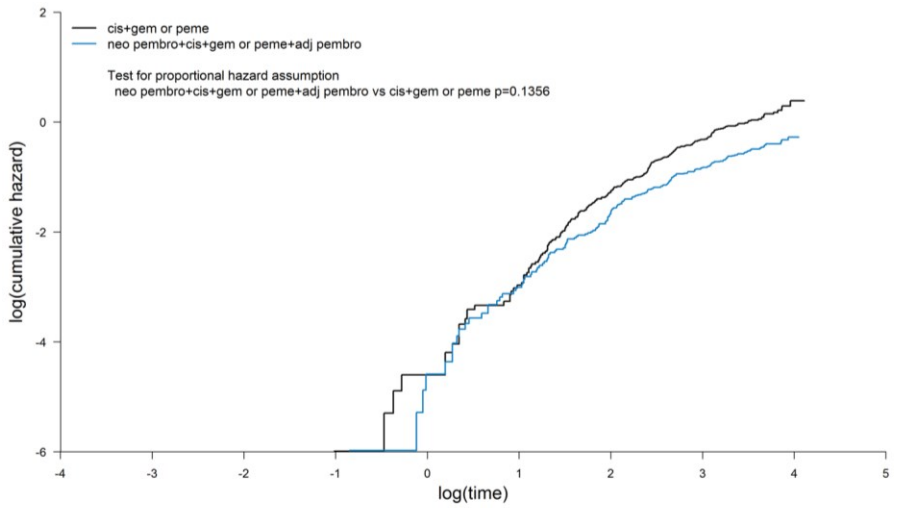
KEYNOTE-671

A



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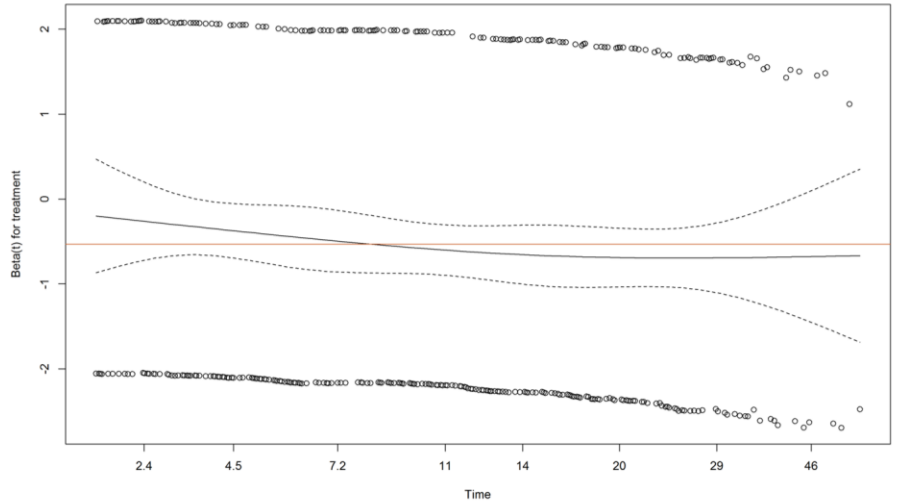

Checkmate-816

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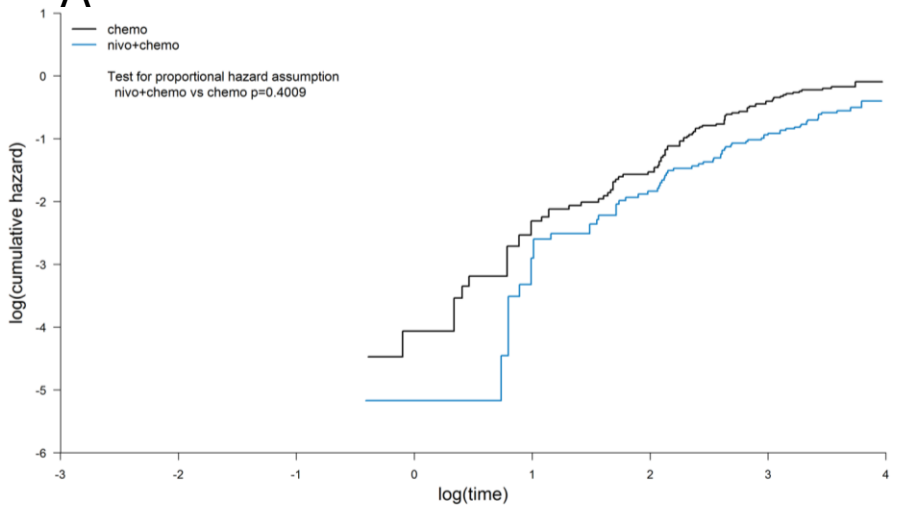

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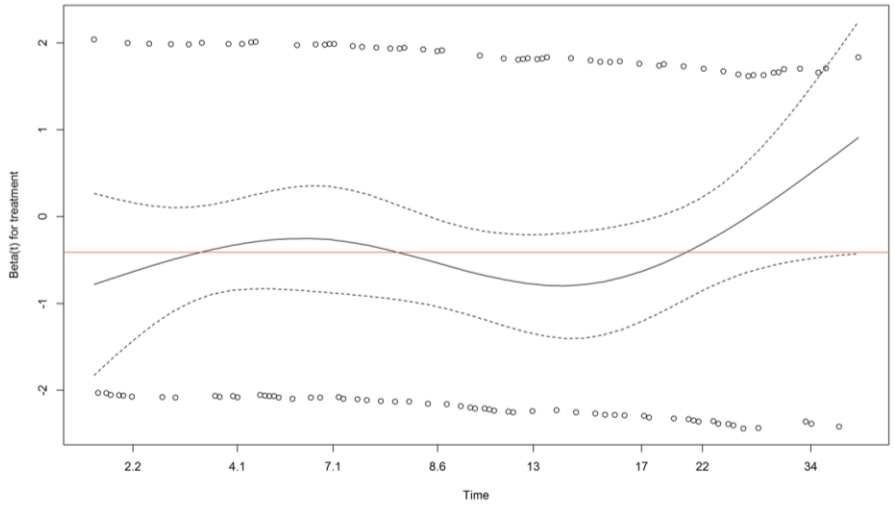


Abbreviations: EFS, event free survival; KM, Kaplan-meier; mITT, modified intention to treat;
A) Log-cumulative hazard plots; B) Schoenfeld residual
*Full assessment of proportional hazards can be seen in response to clarification question A6 (page xx of committee papers)

Key Issue: Proportional hazards assumption (ii)

Back to key issue

Trial	Treatment comparison	Outcome	Grambsch & Therneau test, p-value	Wald test, p-value
CheckMate-816	nivo vs. chemo	EFS	0.4009	0.3741
CHEST	chemo vs. surgery	PFS	0.4913	0.3351
Felip 2010	chemo vs. surgery	DFS	0.0316	0.0124
KEYNOTE-671	pembro vs. chemo	EFS (IA)	0.1356	0.1273
		EFS (BICR)	0.2276	0.2174
Pisters 2010	chemo vs. surgery	PFS	0.0173	0.0109

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

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	Extracted from KEYNOTE-671
Intervention efficacy	EFS curve for perioperative pembrolizumab extrapolated with cause specific distributions.
Comparator efficacy	EFS curves for neoadjuvant nivolumab and surgery alone generated using hazard-ratios versus perioperative pembro from NMA (time-varying in base case)
Efficacy in downstream states	Transitions out of LR/P informed by extrapolations of KEYNOTE-671 aligned sample from SEER database (cause specific and assumed the same for all arms of model) Transitions out of DM informed using market share weighted weekly rates derived from pivotal trials. HCRU costs & utilities applied by to proportion of PF/PD
Utilities	Utilities for EFS, LR/P and DM (pre-progression) sourced from KEYNOTE-671. Post progression from KEYNOTE-407 (squamous) and KEYNOTE-189 (non-squamous)
Costs	NHS reference prices 2021/22, BNF 2023, eMIT and PSSRU
Resource use	Health state resource use extracted from SLR
Etc.	

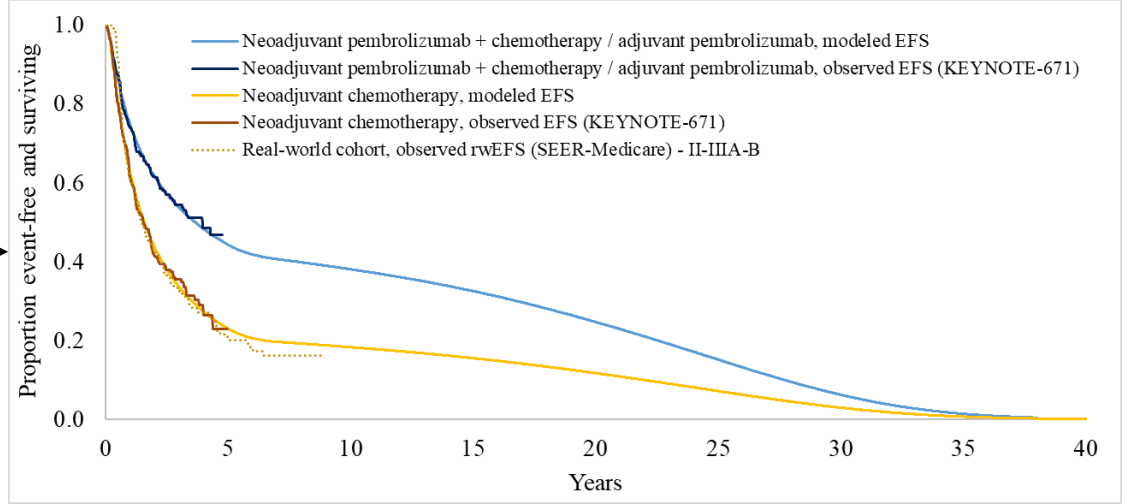
Back to model overview

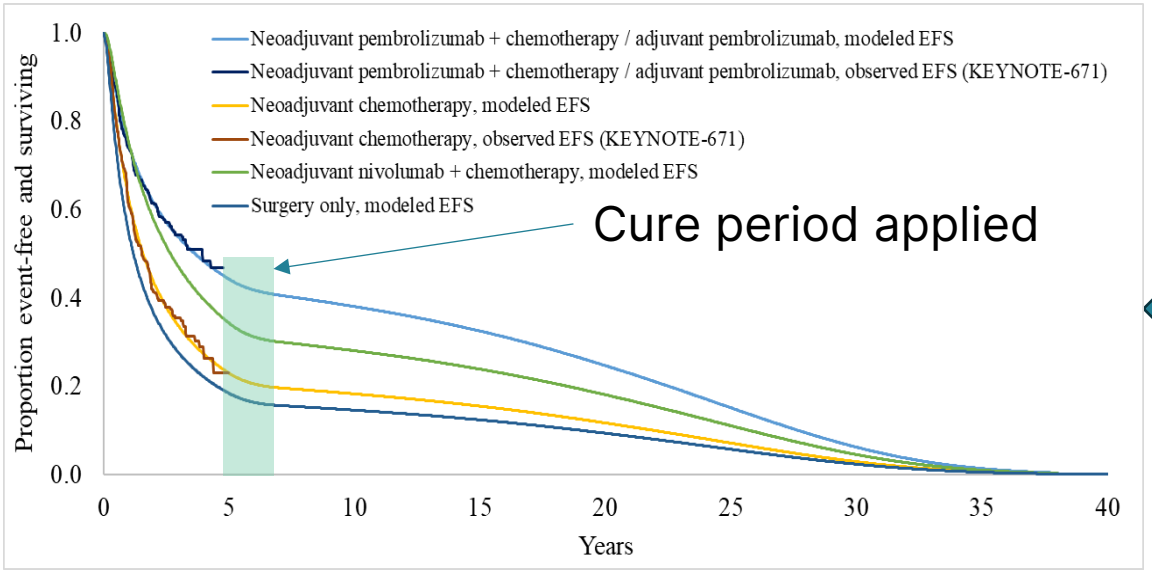
Abbreviations: EFS, event-free survival; NMA, network meta-analysis; LR/P, locoregional recurrence or progression; DM, dsitand metastases; BNF, British National Formulary; PSSRU, personal social services research unit; SLR, systematic literature review

Company's model overview – Modelling efficacy at EFS

EFS curves from both arms of KEYNOTE-671 censored for other events to give separate curves to LR/P, DM and death extrapolated to time horizon of model.

	Parametric distribution		
	EF to LR/P	EF to DM	EF to death
Base case	Gen gamma	Gen gamma	Log-normal





Time-varying hazard ratios applied to perioperative pembrolizumab EFS curve

- breakdown of EFS events assumed to be the same as for perioperative pembrolizumab
- Time-varying HRs applied until 5.2 years then fixed

Back to model overview

Abbreviations: Event-free survival; EF, event free; LR/P, locoregional progression or recurrence; DM, distant metastases; HR, hazard ratio

Company's model overview – Modelling efficacy at LR/P

Sample of the SEER Medicare dataset used to generate transitions from LR/P

- SEER Medicare database patients who were aligned with KEYNOTE-671 population selected (N=43)
- Exponential competing risks models fitted to cause specific transitions from LR/P to DM and death (gives constant weekly rate).
- Transition probability to death state constrained to be as high as general population mortality
- The same transition probabilities out of the LR/P state are applied to all arms of the model

	LR/P to DM	LR/P to death
	Weekly exponential rate	Weekly exponential rate
SEER Medicare KN671-matched cohort (per weekly cycle)	[redacted]	[redacted]

Back to model overview

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)

Transition probabilities weighted by market share of 1L metastatic treatments (2L treatments only incur costs)

- Proportions of 1L and 2L treatments obtained from clinical expert advisory board (see table below)
- Population in DM split into those eligible for treatment with IOs and those ineligible (due to retreatment restriction)
- People eligible for targeted treatment assumed to have efficacy and costings associated with osimertinib (for simplicity)

Metastatic regimen (reference treatment)	IO	No-IO	Weekly rate	
			OS	PFS
Pembrolizumab + (PDC) Δ	24%	0%	0.0073	0.0176
Pembrolizumab + PlatinumΔ	33%	0%	0.0093	0.0198
OsimertinibΔ	15%	15%	0.0041	0.0084
PembrolizumabΔ	23%	0%	0.0080	0.0245
AtezolizumabΔ	6%	0%	0.0079	0.0197
			HR OS	HR PFS
Carboplatin and paclitaxel*	0%	49%	1.67	2.00
Pemetrexed PDC‡	0%	36%	1.41	1.61

Market share weighted

	OS	PFS	PFS/OS
IO	140	60	0.43
No-IO	104	43	0.42

Ratio informs HCRU costs and utility

Converted to weekly failure rate +/- modifier

	OS
IO	0.0076
No-IO	0.0102

- Weekly rates of OS and PFS failure calculated for five 1L reference treatments[Δ] from median OS and PFS
- Total expected PFS and OS in DM in weeks calculated (HRs used from the relevant trials for non-reference chemotherapy treatments[*,‡])
- Total expected OS and PFS weeks for IO eligible and ineligible people was calculated weighted by market share
- Ratio of PFS to OS calculated to inform the proportion of DM who incur pre and post progression utilities and costs
- Total weighted expected OS converted back to weekly rate to inform TPs for leaving DM each cycle

Abbreviations: 1L, first-line; 2L, second-line; IO, immuno-oncology; OS, overall survival; PFS, progression free survival; TP, transition probability
HRs for chemo regimens applied to pembrolizumab regimens from KEYNOTE-189* and KEYNOTE-407**

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

First-line metastatic treatments for efficacy (PFS/OS) and costs

Metastatic regimen (reference treatment)	% IO-eligible	%IO-ineligible	Indicated population	Exponential weekly rate	
				OS	PFS
Pembrolizumab + (PDC) Δ	24%	0%	Non-squamous NSCLC	0.0073	0.0176
Pembrolizumab + PlatinumΔ	33%	0%	Squamous NSCLC	0.0093	0.0198
OsimertinibΔ	15%	15%	Assumed efficacy for all TKIs	0.0041	0.0084
PembrolizumabΔ	23%	0%	PD-L1 ≥ 50% NSCLC	0.0080	0.0245
AtezolizumabΔ	6%	0%	PD-L1 ≥ 50% NSCLC	0.0079	0.0197
				HR OS	HR PFS
Carboplatin and paclitaxel*	0%	49%	Squamous	1.67	2.00
Pemetrexed PDC⁑	0%	36%	Non-squamous	1.41	1.61

Second-line metastatic treatments affect costs only assumed not to affect survival

Second line:	IO-eligible (2L)	IO-ineligible (2L)	IO-eligible (2L)	IO-eligible (2L)
Docetaxel	30%	30%	30%	30%
Pemetrexed + platinum	30%	30%	30%	30%
No active treatment (BSC)	40%	40%	40%	40%

NICE Abbreviations:

Back to model overview

Calculation of standardised mortality ratio (SMR)

- Conditional 5 year survival from Janssen-Heijnen study was weighted by the assumed proportion of patients from KEYNOTE-671 in the relevant disease stage and age groups.
- KEYNOTE-671 patients were assumed to be split 50/50 between the two age groups
- This gave a weighted conditional 5 year survival rate of 65.4%
- The 95% survival rate was divided by the conditional 5 year survival rate of 65.4% to give the SMR of 1.453 which was applied in the model.

Disease stage	Age group	Conditional 5-year relative survival at 5 years	Assumed proportions KEYNOTE-671 trial	Weighted conditional 5-year relative survival rate
2	45-59 years	78%	14.85%	65.4%
	60-74 years	64%	14.85%	
3	45-59 years	68%	35.15%	
	60-74 years	58%	35.15%	

Comparison of cure with previous appraisals (for information only)

Conclusions from prior early stage appraisals in NSCLC

- 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 CDF exit (ID5120)	Perioperative durvalumab (ID6220)
Cure point (CS)	5 years	5 to 7 years, linear reduction. (clinical opinion)	Warm up included (from 4 years)	5 years
Cure proportion	91.5%	0% (5 years) 95% (7 years)	0% (4 years) 95% (5/8 years AM/Osi)	95%
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 on ICER.	EAG attempted MCM but data too immature for osimertinib.	Considered cure was uncertain. Included EAG base cases with and without cure.
Committee conclusion	Significant uncertainty. Considered both EAG approaches. (rec into CDF)	Committee concluded that the cure assumption applied was uncertain but explored sufficiently.	Committee concluded MCM would have been preferable. Warm up should not be applied.	Concluded appropriate to mode cure in some form. Ideally informed by clinical data. Requested cure point and proportion scenarios.

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

Model outputs

Abbreviations: EFS; event-free survival; LR/P, locoregional recurrence or progression; DM, distant metastases