Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer

For public –CON information redacted

Technology appraisal committee D 12 Feb 2025

Chair: Raju Reddy

Lead team: Paul Caulfield (lay), Ben Searle (clinical), Sofia Dias (cost)

External assessment group: Kleijnen Systematic Reviews

Technical team: Emma Bajela, Sam Slayen, Ian Watson

Company: Johnson & Johnson

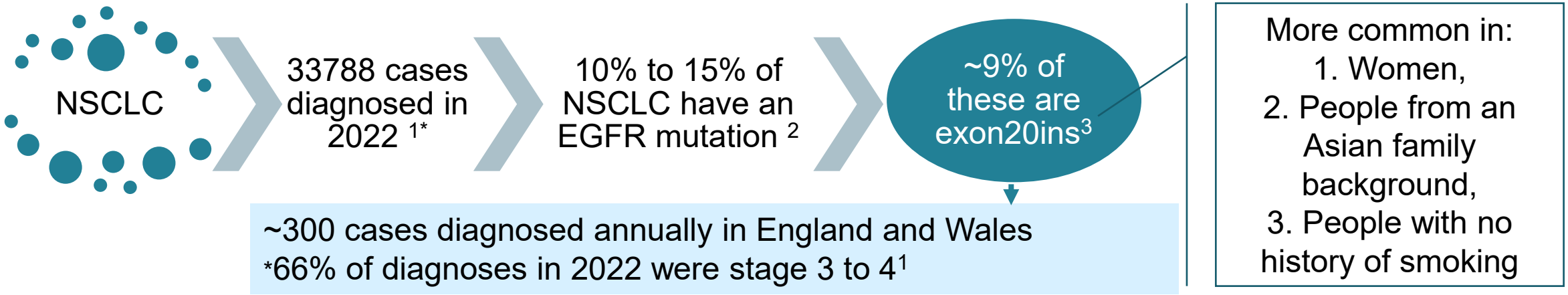
Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer

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

NICE National Institute for Health and Care Excellence

Background on Non small cell lung cancer

EGFR exon20 insertion positive disease is a rare subset of NSCLC



- **Epidemiology, classification, causes**
- NSCLC 1 of 2 major subtypes of lung cancer and accounts for ~90% of all lung cancers [2]
- Diagnosis and staging done by histological and genetic testing of biopsy samples
- Typically classified based on mutations present; EGFR gene mutations among the most common
- Common EGFR activating mutations include Exon19 deletions or L858R point mutation on Exon21
- Exon20 insertions are less common and associated with EGFR-TKI resistance

Abbreviations: EGFR; epidermal growth factor receptor, NSCLC; non small cell lung cancer, exon20ins, exon 20 insertions; exon20 insertion, TKI; tyrosine kinase inhibitors

1. Royal College of Surgeons of England (2024). National Lung Cancer Audit: state of the nation report 2024, version 2.available at https://www.lungcanceraudit.org.uk/wp-content/uploads/2024/05/NLCA-State-of-the-Nation-2024_16.05.24_V2.0.pdf (accessed Jan 2025)
2. EGFR+ UK. About lung cancer EGFR stands for epidermal growth factor receptor. | EGFR Positive UK (accessed Jan 2025)
3. Van Sanden et al. Prevalence of Epidermal Growth Factor Receptor Exon 20 Insertion Mutations in Non-small-Cell Lung Cancer in Europe: A Pragmatic Literature Review and Meta-analysis. Target Oncol. 2022 Mar

Patient perspectives (EGFR+ UK and RCLCF)

Exon20 positive disease has a large impact and limited treatment options

Effects on quality of life

- EGFR exon20 mutation positive NSCLC generally affects more younger people, non-smokers and females (often still working and with dependent children) than other lung cancers.
- Diagnosis particularly devastating, often a total shock. Many people are diagnosed at Stage 4, and are often unable to work as a result of their treatment
- Psychological burden includes fear of progression or recurrence after treatment, and anxiety around treatment options

Treatment options

- There are limited treatment options available for exon20 insertion positive NSCLC

"It all feels so alienating. Both because my friends who don't have cancer just don't understand how much it affects me. How huge it all is. But I also feel alienated with other lung cancer patients, because most people have the Exon 21 mutation and take osi, and don't understand that that's not possible for me. It's just so scary."

NICE

Abbreviations: EGFR; epidermal growth factor receptor, NSCLC; non small cell lung cancer, RCLCF; Roy castle lung cancer foundation, OSI; osimertinib

Clinical perspectives- British Thoracic Oncology Group

Large unmet need

Treatment and unmet need

- Large unmet need as there are no targeted therapies for this population in NHS
- There is some use of post-chemotherapy immunotherapy although the effectiveness of checkpoint inhibitors in this group is uncertain
- Longer chair time (2 hours) to infuse amivantamab compared to current practice

"There is no current targeted therapy available for patients with NSCLC harbouring EGFR EXON 20 insertion"

Testing for EGFR exon20 insertions

- Available and funded for all people, full NGS testing is increasing but not currently consistently delivered (some labs still carry out limited panel testing)
- If approved there will need to be efforts to ensure NGS testing identifies all people (currently up to 30% of cases might not be identified)
- NHSE ctDNA testing could help improve pick up of EGFR exon 20 insertions

"Amivantamab would be a step change in treatment for these patients"

NICE

Abbreviations: EGRF; epidermal growth factor, NSCLC; non small cell lung cancer, NGS; next generation sequencing, ctDNA; circulating tumour DNA

Equality considerations

Equality issues highlighted during appraisal:

- EGFR exon 20 insertion mutations are more common in women and in people of Asian heritage and people with no history of smoking

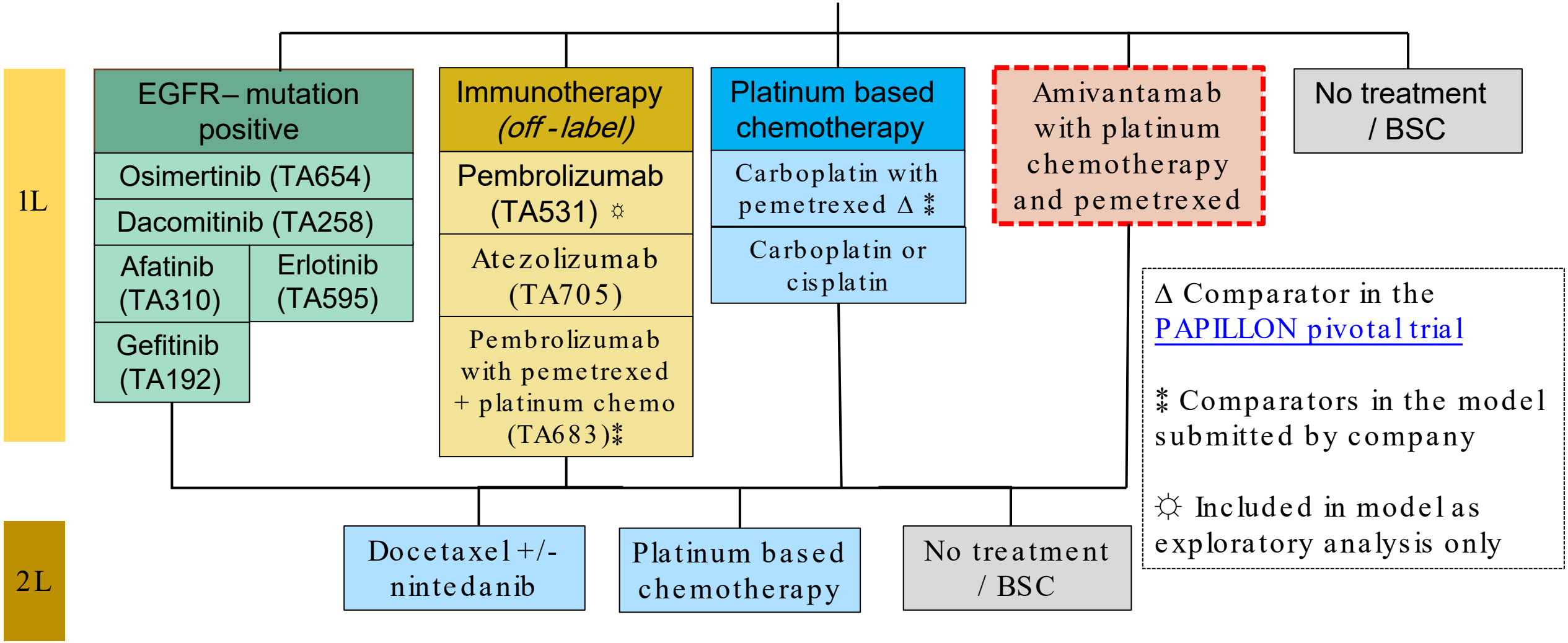
- There are concerns that lung cancer and the symptoms of lung cancer are associated with stigma, particularly in Asian communities, which could contribute to diagnosis or treatment delaying behaviour

- Asian people make up 9% of the population in England and Wales (ONS, 2021) and 61% of population in the PAPILLON trial for amivantamab with chemotherapy were Asian

Abbreviations: ONS; office for national statistics

Treatment pathway – Untreated EGFR exon20+ NSCLC

Numerous options for NSCLC and EGFR+ disease but limited options for exon20+



Abbreviations: EGFR; epidermal growth factor receptor, exon20+; exon 20 insertion mutation positive, NSCLC; non small cell lung cancer, BSC; best supportive care

Notes: 1L immunotherapy licences exclude EGFR positive NSCLC; post chemotherapy immunotherapy options not shown (e.g TA428)

Amivantamab (Rybrevant, Johnson & Johnson)

Amivantamab offered until progression (post-progression use allowed in trial)

Marketing authorisation	• In combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations • UK MA granted July 2024
Mechanism of action	• Binds EGFR and MET receptors to disrupt signalling functions • This enhances degradation of EGFR and MET, reducing tumour growth and progression
Duration of treatment	• Amivantamab 'until disease progression or unacceptable toxicity' • Pemetrexed to disease progression • Platinum based chemotherapy every 3 weeks for up to 12 weeks
Administration	• Intravenous infusion • Dosage (body weight at baseline) ➢ Less than 80kg: 1400 mg (4 vials) weekly for first 4 doses then 1750 mg every 3 weeks ➢ 80kg or above: 1750 mg weekly (5 vials) for first 4 doses then 2100 mg every 3 weeks
Price	• Amivantamab 350mg per 7ml vial • List price £1,079.00 per vial • A confidential discount is in place for amivantamab

Abbreviations: NSCLC; non small cell lung cancer, EGFR; epidermal growth factor receptor, MA; marketing authorisation, MET; MET proto-oncogene

Key issues

Issue	Resolved?	ICER impact
Comparators (scoped comparators and blended comparator)	No	Large
Validity of ITC – adjustment for variables in propensity score weighting	No	Unknown
ITC - lack of sensitivity analyses for base case ATT	No	Unknown
ITC - lack of adjustment for pembrolizumab monotherapy	No	Unknown
Extrapolating longer term effects (TTDD and OS)	No	Large
Treatment effect waning	No	Unknown
Dosing and vial sharing	No	Moderate
Adverse event costs	No	Small
Plausibility of extrapolated benefits	No	Unknown

Other issues

Issue	Resolved?	ICER impact
Squamous histology	No	Unknown
Health state utilities	No	Small
Validation of model	No	Unknown

Abbreviations: ITC; indirect treatment comparison, ATT; average treatment effect for the treated, TTDD; time to treatment discontinuation or death, OS; overall survival, ICER; incremental cost effectiveness ratio

Key issues: Comparators

ICER Impact: Large

Estimates of treatments in current NHS practice vary and uncertainty around how to model them

Background

- Company excluded several scoped comparators: (EGFR TKIs, atezolizumab)
- Company considers platinum-based chemotherapy and pembrolizumab + platinum-based chemotherapy relevant
- Company chose blended comparator approach instead of fully incremental analyses, which assumes 70% chemotherapy and 30% pembrolizumab with chemotherapy
- EGFR+ UK survey suggests current NHS care is 70% chemotherapy/30% TKIs (mainly Osimertinib) and no IOs

Company

- Prefer to use clinical opinion for comparator choice (pembrolizumab only included as exploratory comparator)
- Blended approach justified as no established practice and no relevant guidelines for untreated exon20+ NSCLC
- Different comparator distributions in blended comparator explored in scenario analyses

EAG comments

- Company should include all treatments used in NHS clinical practice
- EAG clinical expert: 60% carboplatin with pemetrexed, 10% carboplatin/cisplatin, 30% pembrolizumab with carboplatin and pemetrexed used in NHS practice
- Blended comparator approach can hide important differences in estimated cost effectiveness
- EAG prefer to model comparisons with each comparator separately

What are the most appropriate comparators for amivantamab-chemotherapy?
How should those comparators be modelled (blended comparator or separately)?

Abbreviations: NSCLC; non small cell lung cancer, TKI; tyrosine kinase inhibitor, EGFR; epidermal growth factor, NCRAS, National Cancer Registration and Analysis Service, IO; Immunotherapy

Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer

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

NICE National Institute for Health and Care Excellence

Key clinical trial – PAPILLON

Back to treatment pathway

Includes only 1 of comparators; cross-over permitted; treatment beyond progression 'allowed'

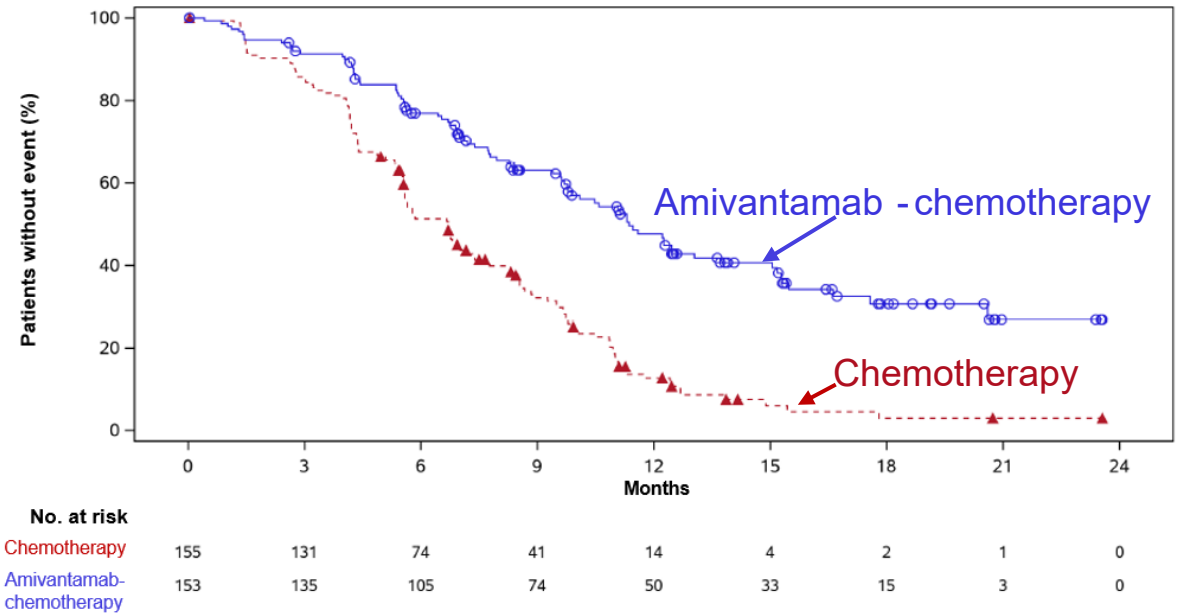
Design	Phase 3, multicentre, randomised, open label superiority
Population	Adults with untreated EGFR Exon 20 insertion mutation-positive advanced NSCLC (N=308)
Intervention	Amivantamab with pemetrexed and carboplatin (amivantamab-chemotherapy) n=153
Comparator	Carboplatin with pemetrexed (chemotherapy) n=155
Duration of treatment	Carboplatin- up to 4 cycles (12 weeks) Pemetrexed – with carboplatin for 4 cycles then 'maintenance' until disease progression Amivantamab – 'Continuation of study treatment after disease progression may be allowed'
Median treatment duration	Amivantamab arm: 9.72 months Chemotherapy arm: 6.74 months
Primary outcome	Progression free survival (PFS) blinded review RECIST criteria
Key secondary outcomes	Overall response rate (ORR), duration of response, overall survival (OS), time to subsequent treatment (TTST), progression free survival 2 (PFS2)
Analyses for OS	Interim: at primary analysis of PFS, p needs to be <0.0008 Final: at ~ 200 deaths, p needs to be <0.0498
Locations	131 sites in 25 countries including UK (3 sites)
Ethnicity	61% Asian, 33% White,1% Black

Abbreviations: EGFR; epidermal growth factor, NSCLC; non small cell lung cancer, RECIST; response evaluation criteria in solid tumours, PFS; progression free survival, ORR; overall response rate, OS; overall survival, TTST; time to subsequent treatment

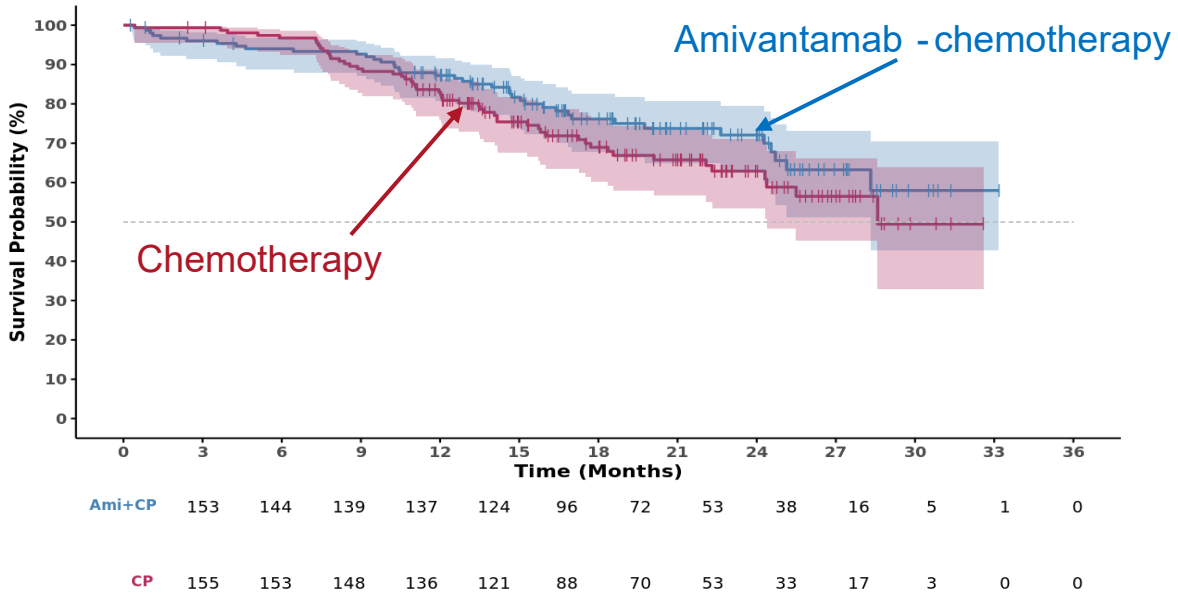
Key trial results – PAPILLON overall and progression free survival

Amivantamab-chemotherapy improves PFS compared to chemotherapy

Amivantamab-chemotherapy vs chemotherapy PFS (May 2023 DCO)



Amivantamab-chemotherapy vs chemotherapy OS (Oct 2023 DCO)



HR (95% CI)	0.40 (0.30 to 0.53)

HR (95% CI), unadjusted	0.76 (0.50 to 1.14)
HR (95% CI), when IPCW adjusted (for treatment switching)	[redacted]

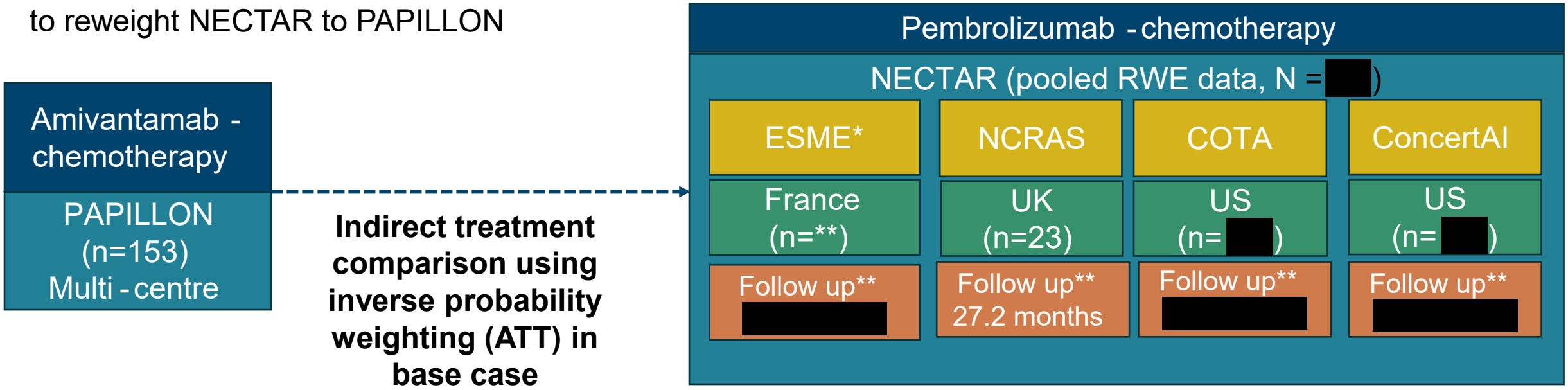
NICE

Abbreviations: PFS; progression free survival, BICR; blinded independent central review, OS; overall survival, HR; hazard ratio, CI; confidence interval, RPSFT; rank preserving structural failure time; DCO, data cut off

Indirect treatment comparison

Company used indirect treatment comparison to compare to pembrolizumab-chemotherapy

- NECTAR study gathered IPD from real-world registries to inform outcomes and baseline characteristics for pembrolizumab-chemotherapy [redacted] had pembrolizumab-chemotherapy)
- Data from the amivantamab-chemotherapy arm of the PAPILLON trial (n=153)
- Prognostic factors in advanced NSCLC ranked based on a literature review and expert validation and used to reweight NECTAR to PAPILLON



Abbreviations: IPD; individualised patient data, ITC; indirect treatment comparison, RWE; real world evidence, NSCLC; non small cell lung cancer, SLR; systematic literature review, PW; Inverse probability weighting, ATT; average treatment effect for the treated,

*ESME -Indirect IPD, ** Median follow up shown

ITC Results (Overall survival)

Amivantamab-chemotherapy (ACP) showed statistically significant improvement in OS compared to pembrolizumab-chemotherapy (pembro-CP), for both unadjusted and adjusted analyses

Unweighted and ATT weighted OS KM curves for ACP vs pembro-CP (NECTAR study)

[redacted]

Summary of Indirect treatment comparison OS results for ACP vs pembro-CP

Outcome	Unadjusted analysis		ATT-adjusted analysis	
	Median, months (95% CI)	HR (95% CI)	Median, months (95% CI)	HR (95% CI)
ACP	[redacted]	[redacted]	[redacted]	[redacted]
Pembro-CP	[redacted]	[redacted]	[redacted]	[redacted]

NICE Abbreviations: ACP; amivantamab chemotherapy, OS; overall survival, ATT; average effect of the treated, KM; Kaplan meier, CP; chemotherapy, HR; hazard ratios, CI; confidence intervals, NE; not estimable

ITC Results (Time to next treatment)

Amivantamab-chemotherapy (ACP) showed statistically significant improvement in TTNT compared to pembrolizumab-chemotherapy (pembro-CP), in both unadjusted and adjusted analyses

Unweighted and ATT weighted TTNT KM curves for ACP vs pembro-CP (pooled RWE)

[redacted]

Summary of Indirect treatment comparison TTNT results for ACP vs pembro-CP

Outcome	Unadjusted analysis		ATT-adjusted analysis	
	Median, months (95% CI)	HR (95% CI)	Median, months (95% CI)	HR (95% CI)
ACP	[redacted]	[redacted]	[redacted]	[redacted]
Pembro-CP	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACP; amivantamab chemotherapy, TTNT; time to next treatment, ATT; average effect of the treated, KM; Kaplan meier, CP; chemotherapy, HR; hazard ratios, CI; confidence intervals, NE; not estimable

Key issues: ITC - propensity score weighting

ICER Impact: Unknown

Real world data at risk of confounding when comparing amivantamab + chemotherapy to pembrolizumab+ chemotherapy

Background

- Company used propensity score weighting to estimate the average treatment effect (ATT)
- Company chose 8 baseline prognostic characteristics but only used 5
- Did not adjust for Asian ethnicity (66% in PAPILLON, [redacted] in NCRAS), other metastatic locations, and smoking history

Company

- Included all variables commonly available across databases in the analysis (three excluded variables not available in all studies, see slide on propensity score weighting)
- In a non-randomised comparison adjusting for variables cannot entirely remove residual confounding bias

EAG comments

- Unclear whether 3 excluded variables were balanced between PAPILLON and NECTAR study cohorts which adds uncertainty. Suggest adjusting for all relevant prognostic variables in the base case
- EAG base case uses NECTAR ATT ITC analysis – only option for the data available
- Impact on ICERs of failing to adjust for excluded variables is unknown

What is the committee's view on the propensity score weighting in the ITC?

Abbreviations: ITC; indirect treatment comparison, PSW; propensity score weighting, SLR; systematic literature review, ATT; average treatment effect of the treated, ICER; incremental cost effectiveness ratio

Key issues: ITC- sensitivity analyses and pooling data

ICER Impact: Unknown

There is uncertainty linked to the lack of sensitivity analyses in the base case ITC and the approach to pooling data

Background

- Company did not do sensitivity analyses by using alternative adjustment methods such as regression or a doubly robust method for the full ATT analyses which they use in base-case.
- EAG has concerns about how the data from different registries was pooled for the NECTAR study. Multi-level structure of data (e.g. coming from multiple sources and countries) should have been considered

Company

- Suggested methods require centralised pooling of IPD. Not possible due to the remote access setup of the ESME IPD, but could be carried out using the NCRAS UK data (see sensitivity analysis results slide)
- This would not be feasible for a specific class (e.g. pembrolizumab-chemotherapy) due to limited sample, but was done for the entire NCRAS sample of 23 patients (Scenario 11)
- Didn't use multi-level pooling approach. Present results accounting for within patient and source correlation.

EAG comments

- Results of sensitivity analysis using only UK data consistent with ATT analysis which is reassuring but lack of sensitivity analyses for full NECTAR ITC (used in company and EAG base cases) brings uncertainty.
- Company's lack of consideration of multi-level structure of data may bias ITC and associated with uncertainty

What is the committee's view on the indirect treatment comparisons?

NICE

Abbreviations: ITC; indirect treatment comparison, ATT, average treatment effect of the treated, IPD; individualised patient data, NCRAS, national cancer registry and analysis service

Key issues: ITC- Pembrolizumab monotherapy

ICER Impact: Unknown

There is a lack of supporting information and adjustment for the ITC comparing to pembrolizumab monotherapy

Background

- Company presented ITC to inform pembrolizumab monotherapy comparison, this used the "immunotherapy alone" class from the NECTAR study of which [redacted] had pembrolizumab
- TTNT hazard ratio ([redacted]); OS hazard ratio ([redacted])
- Company only presented unadjusted ITC analysis comparing amivantamab-chemotherapy with pembrolizumab monotherapy (did not use ATT adjustment or alternative methods)

Company

- Did not use ATT adjustment due to small numbers in immunotherapy alone treatment group.

EAG comments

- Given lack of adjustment there are considerable uncertainties on ITC analysis results (ICER impact is unknown)

Is the ITC comparing amivantamab-chemotherapy to immunotherapy monotherapy suitable for decision making?

Abbreviations: ITC; indirect treatment comparison, ATT; average treatment effect of the treated, ICER; incremental cost effectiveness ratio

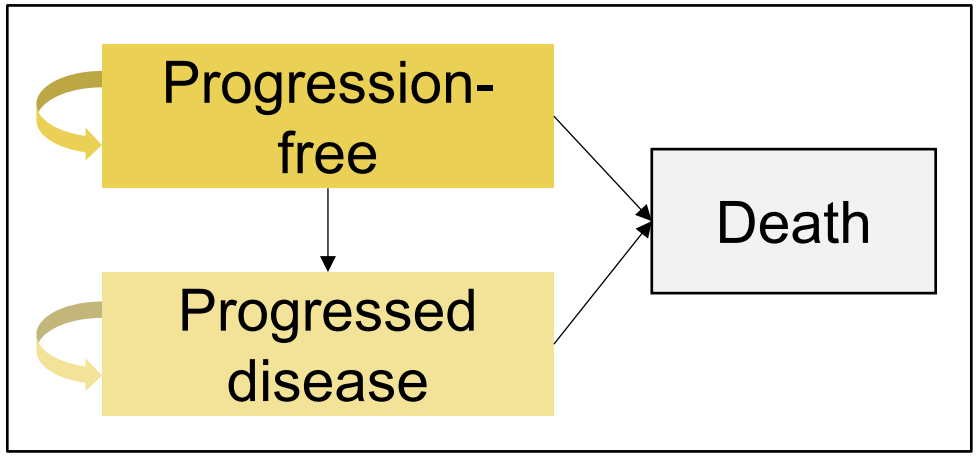
Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer

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

NICE National Institute for Health and Care Excellence

Company's model overview

Model structure:
Partitioned survival



Technology affects **costs** by:

- Increased acquisition costs of amivantamab with chemotherapy
- Increased resource use of the progression free state for amivantamab with chemotherapy
- Increased resource use of the progressed disease state for amivantamab with chemotherapy

Technology affects **QALYs** by:

- Increased health state occupancy duration in the progression free and progressed disease health states

Assumptions with **greatest ICER effect**:

- Blended comparator compared to fully incremental analysis
- Alternative proportions in blended comparator (increasing IO usage reduces ICER)
- NCRAS data to model comparator efficacy and treatment distribution
- Choice of distribution for Amivantamab with chemotherapy OS extrapolation
- Alternative distributions for TTDD extrapolation

Abbreviations: QALY; quality adjusted life year, ICER; IO; immunotherapy incremental cost effectiveness ratio, OS; overall survival, NCRAS national cancer registry and analysis service, TTD; time to treatment discontinuation

How company incorporated evidence into model

Input and evidence sources

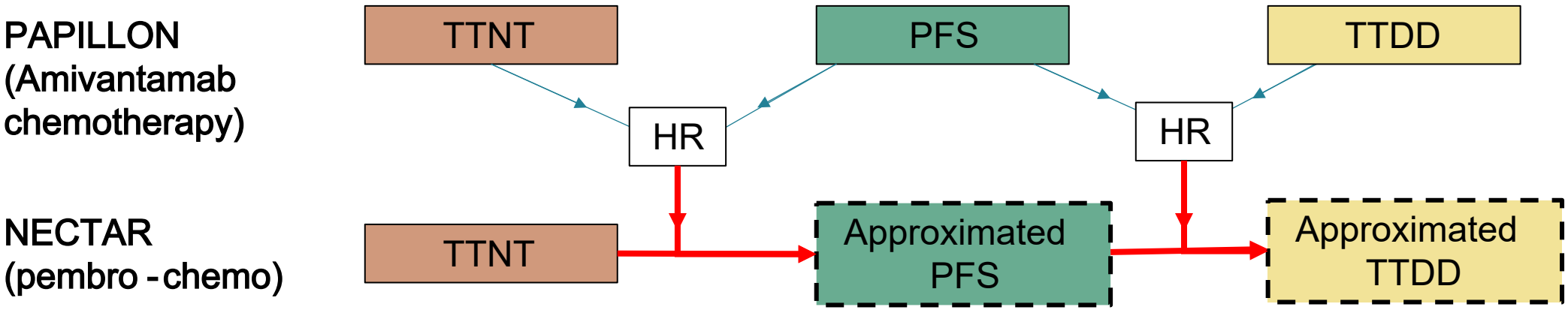
Input	Assumption and evidence source
Baseline characteristics	PAPILLON and literature
Intervention efficacy	PAPILLON (PFS, OS and TTDD)
Comparator efficacy	Chemotherapy – PAPILLON (PFS, OS and TTD) Pembrolizumab with chemotherapy NECTAR RWE (adjusted with ATT weighting) - TTNT used to approximate PFS (TTNT>PFS HR from PAPILLON applied) - TTDD uses further HR of TTDD>PFS from PAPILLON applied to PFS
Utilities	PAPILLON trial EQ5D-5L data (mapped to ED-5D-3L)
Discount rate	3.5%
Time horizon	30 years
Cycle length	1 week
Costs	NHS reference costs costs 2023/23, PSSRU, eMIT, BNF
Resource use	SLR
Severity modifier	Uses baseline characteristics for PAPILLON trial, 1.2X modifier applied

Abbreviations: SLR; systematic literature review, PFS; progression free survival, OS; overall survival, TTD; time to treatment discontinuation, TTDD, time to treatment discontinuation or death; ATT; average treatment effect of the treated, RWE; real world evidence, TTNT; time to next treatment, HR; hazard ratio, PSSRU; Personal Social Services Research Unit, Emit; electronic market information tool, BNF; British national formulary

How company incorporated evidence into model

Company approximated PFS and TTDD for pembrolizumab-chemotherapy

- PAPILLON reported TTNT, PFS and TTDD
- Only TTNT was available from NECTAR. Company approximated PFS and TTDD by applying per cycle HRs from PAPILLON to TTNT and approximated PFS curves.



EAG comments

- Approach to approximate PFS suboptimal as relies on assumption that ratio between TTNT/PFS identical for amivantamab-chemotherapy and pembrolizumab-chemotherapy (different drug classes).
- However, alternative PFS modelling had minimal effect on ICERs. PFS approximation is reasonable.
- Approach to approximate TTDD also suboptimal as relies on similar assumption. This is likely to have [redacted] impact due to the potential effect of TTDD on treatment costs.
- Explore this uncertainty using conservative Gompertz scenario for TTNT and by extension PFS and TTDD

Abbreviations: PFS; progression free survival, TTDD; time to treatment discontinuation or death, TTNT; time to next treatment, ICER; incremental cost effectiveness ratio, HR; hazard ratio

Dashed lines signify "approximated" outcome, not a direct outcome from the NECTAR study.

Extrapolating outcomes beyond end of evidence

EAG chooses different base case models to company for overall survival and to estimate duration of treatment (disagreements or large impact choices highlighted in orange)

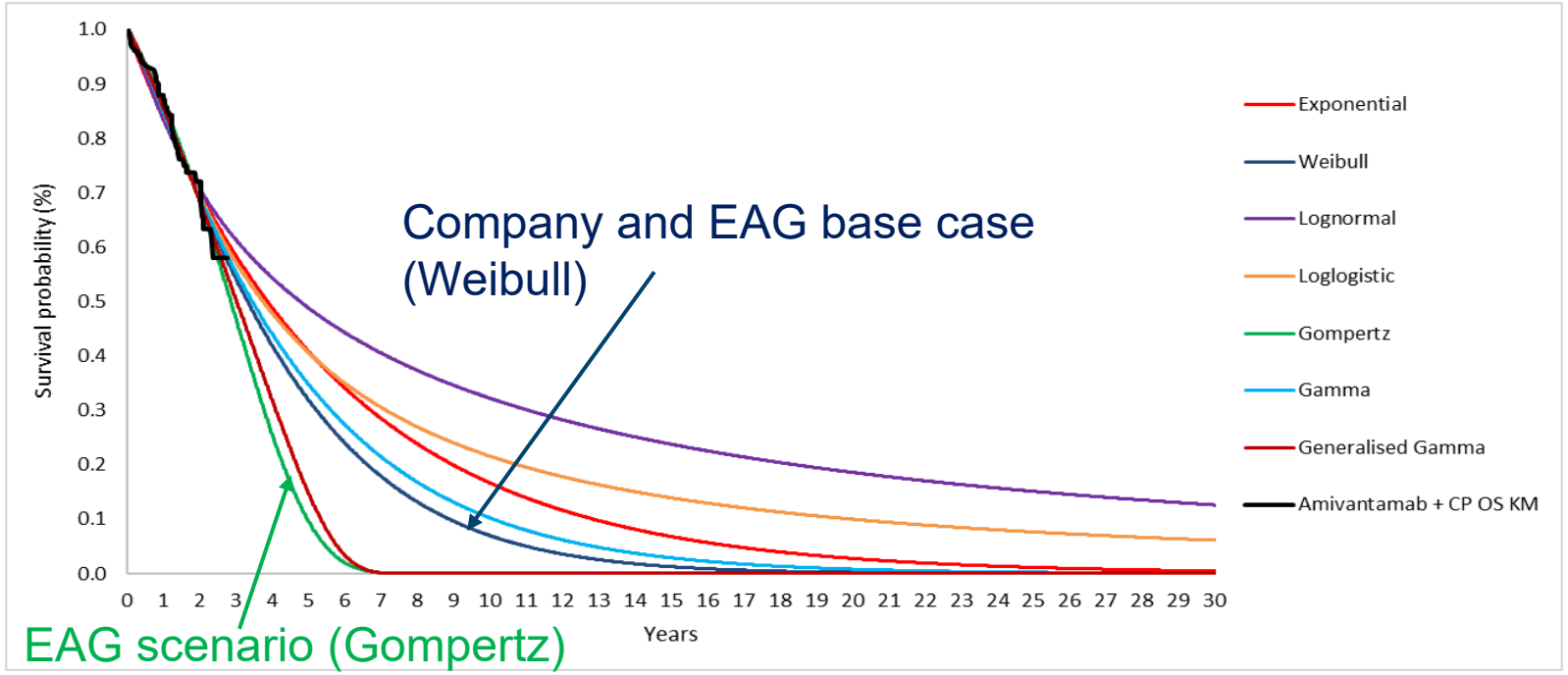
Outcome	Intervention	Company base-case	EAG base-case	Scenarios	Slide #
PFS	Amivantamab-chemotherapy	Gamma	Gamma		
	Chemotherapy	Gamma	Gamma		
	Pembrolizumab-chemotherapy*	Log-logistic	Log-logistic	Gompertz (EAG)	
Overall survival	Amivantamab-chemotherapy	Weibull	Weibull	Gompertz (EAG)	Slide 25
	Chemotherapy	Gamma	Log-logistic		Slide 26
	Pembrolizumab-chemotherapy	Log-logistic	Log-logistic		
Time to treatment discontinuation or death	Amivantamab-chemotherapy	Weibull (ami-chemo) Weibull (chemo)	Log-logistic (ami-chemo) Exponential (chemo)		Slide 27 Slide 28
	Chemotherapy	Gamma	Gamma		
	Pembrolizumab-chemotherapy*	Log-logistic	Log-logistic	Gompertz (EAG)	

Abbreviations: PFS; progression free survival, OS; overall survival, TTDD; time to treatment discontinuation or death
*Note, PFS and TTDD for pembro-chemo are ultimately derived from extrapolation of TTNT from the NECTAR as per previous slide. Distributions for these outcomes actually refer to extrapolation of TTNT.

ICER Impact: Large

Key Issue: OS extrapolation: amivantamab-chemotherapy

Company chooses Weibull, EAG considers it overestimates but uses it for base case



- **Company:** Weibull fits best with clinical expert opinion
- **EAG**: Weibull in base case but uses Gompertz scenario to reflect lower estimates from their expert.
- Any expert opinion should be interpreted with caution due to limited experience with amivantamab in NHS

Source	Median OS	3-year	5-year	10-year
Weibull	39.79	54.37%	32.10%	7.04%
Gompertz	34.27	47.11%	9.87%	0.00%
Company expert	-	-	27.5%	7.5%
EAG expert	-	25-30%	10-15%	unknown

Which distribution should be used to extrapolate amivantamab plus chemotherapy OS?

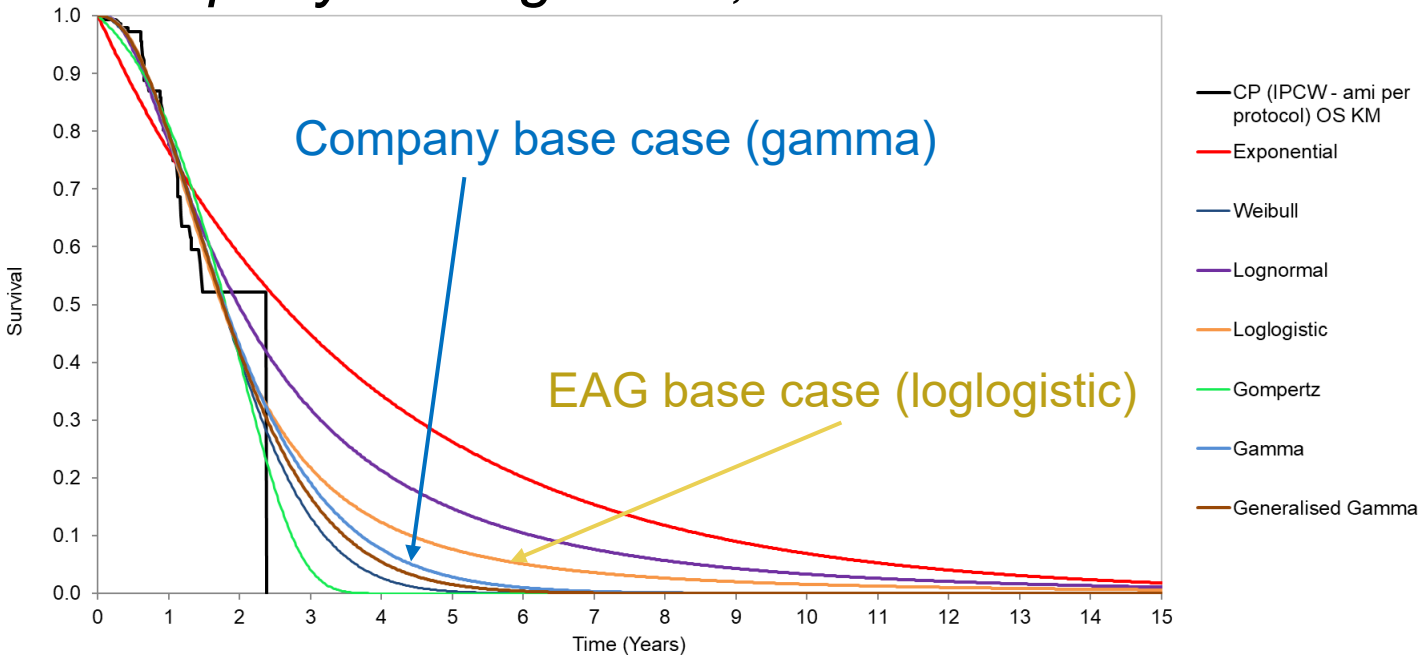
NICE

Abbreviations OS; overall survival

ICER Impact: Large

Key Issue: OS extrapolation: chemotherapy

Company uses gamma, EAG considers it underestimates and uses log-logistic



- **Company** gamma distribution based on clinical plausibility and fit to observed data
- **EAG**: gamma underestimates OS. Adopted log-logistic as better aligned with company and EAG expert opinion.

Source	Median OS	3-year	5-year	10-year
Gamma	21.39	19.27%	2.89%	0.01%
Log-logistic	20.93	21.87%	7.70%	1.58%
Company experts	-	-	10%	1%
EAG expert		20%	5%	<1%

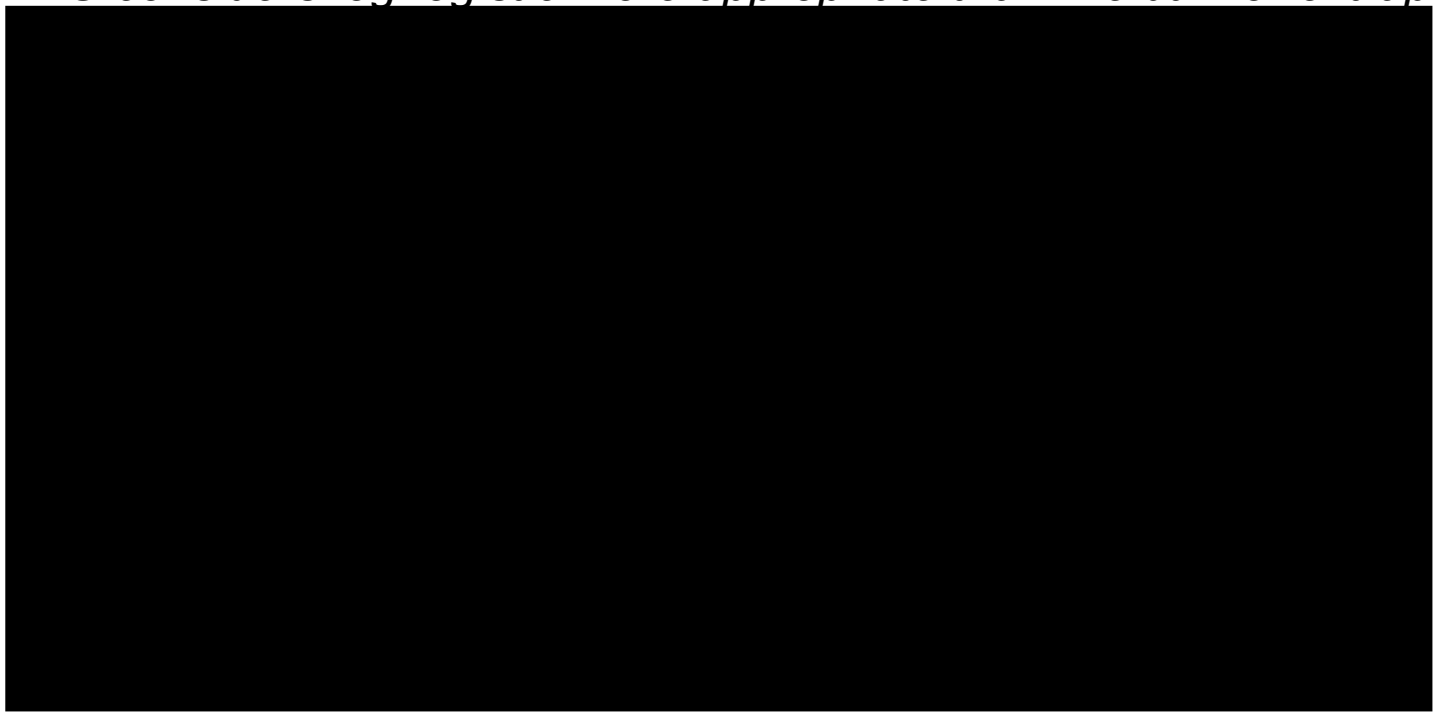
Which distribution should be used to extrapolate chemotherapy OS?

Abbreviations OS; overall survival

ICER Impact: Large

Key Issue:TTDD extrapolation: amivantamab-chemotherapy

EAG considers log-logistic more appropriate than Weibull for extrapolating amivantamab component of intervention



- **EAG:** Weibull substantially underestimates treatment duration based on expert opinion, prefers log-logistic.
- Notes lack of experience with amivantamab in NHS practice

Note: PAPILLON trial allowed continuation of amivantamab after progression

Source	Median TTDD	1-year	3-year	5-year
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Company experts	-	-	35%	5%
EAG expert	-		15-20%	5-10%

Which distribution should be used to extrapolate TTDD for the amivantamab component?

Abbreviations: TTDD; time to treatment discontinuation or death, OS; overall survival

ICER Impact: Large

Key Issue:TTDD extrapolation: amivantamab-chemotherapy

EAG considers exponential more appropriate to Weibull for extrapolating chemotherapy component of intervention

[redacted]

Source	Median TTDD	1-year	3-year	5-year
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Company experts	-	-	10.5%	2.5%
EAG experts	-	-	10-15%	<5%

NICE Which distribution should be used to extrapolate TTDD for the chemotherapy component?

Abbreviations: TTDD; time to treatment discontinuation or death, OS; overall survival

Key issue: Amivantamab treatment effect waning

Lack of exploration of treatment effect waning associated with uncertainty

ICER Impact: Unknown

Background

- Company includes no waning of treatment effect for amivantamab-chemotherapy or exploratory scenarios

Company

- Median PFS of amivantamab-chemotherapy in PAPILLON is 11.4 months, unlikely to be any treatment effect waning in this time and any waning would not have a clinically meaningful impact.
- Committee in TA850 (amivantamab appraisal in treated NSCLC) considered this rationale appropriate also noting that effect waning is usually applied for immunotherapies with stopping rules. (which is not the case with amivantamab)
- Any treatment effect waning would be implicitly captured in the selected curves.

EAG comments

- Assumption of no treatment effect waning is uncertain, exploratory scenarios requested at clarification would have been informative but company did not provide them.

How should the longer term relative treatment effect of amivantamab-chemotherapy be modelled?

Abbreviations: CS; company submission, NSCLC; non small cell lung cancer

ICER Impact: Moderate

Key issue: Dosing & vial sharing

Modelling of dosing frequency and implicit vial sharing could benefit amivantamab

Background

- Company assumes a fraction of a dose given per model cycle, instead of full dose at the start of each cycle then a period of no doses. This doesn't accurately represent practice and may underestimate per-cycle costs
- EAG says company approach also implicitly allows vial sharing for amivantamab as vials not rounded up (e.g patients could have [redacted] units) whereas for pembrolizumab they were rounded.

Company

- The model does not allow vial sharing, fractional values in the number of vials are due to average number of vials being calculated at cohort level and dose reductions (due to weight) mean that some people will have 4 vials (those under 80kg) while others have 5
- Advisory board suggests dose skipping and reductions seen in practice and should be accounted for in model
- Similar dose adjustments accepted in previous NICE appraisals (TA428, TA653, TA654 & TA898)

EAG comments

- Impact of dosing frequency on ICERs is unclear but could benefit amivantamab
- Company applies RDI to units per administration which reduces number of units per administration by <1 vial. Implicit vial sharing benefits amivantamab. EAG base case prevents vial sharing.

How should costs be modelled with respect to dosing frequency?
How should costs be modelled with respect to vial sharing?

Abbreviations: RDI, relative dose intensity, ICER; incremental cost effectiveness ratio

Key issue: Costing of adverse events

Modelled adverse event costs may be underestimated

ICER Impact: Small

Background

- Company adverse event unit costs lower than in other NSCLC appraisals: e.g for anaemia this appraisal costs £739.05 compared to between £978 to £2,692 in TA484, TA520 and TA683.

Company

- Followed a standard costing approach by calculating total costs of all codes of non-elective short stay adverse events from National schedule of NHS costs (2022/2023) and weighting them by total number of those events
- The codes used were in line with those used in prior TAs and were validated with medical opinion

EAG comments

- The company approach uses a weighted average of all cost codes of an adverse event but applies that cost to only Grade 3 and 4 adverse events. This underestimates costs.
- Unclear why costs codes for certain settings were used over others for a given AE, results in uncertainty
- EAG base case includes only unit costs for the severest versions of AEs for non-elective short stay (in line with the modelling)
- EAG scenario explores most severe costs for all AEs, not just short stay

How should AE costs be modelled?

Abbreviations: NSCLC; non small cell lung cancer, AE; adverse event, ICER; incremental cost effectiveness ratio

ICER Impact: Unknown

Key issue: Plausibility of extrapolated benefits

Background

- Majority of LY and QALY gains [redacted] occur in the progressed disease health state for both intervention and comparators, but treatment continued until disease progression

	Amivantamab -chemotherapy	Chemotherapy		Pembrolizumab -chemotherapy	
	Absolute	Absolute	Increment	Absolute	Increment
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Expect majority of gains would be in the progression free state for treatments that are only given until progression
- [redacted] of LYG are accrued in the extrapolated period of the model
- Requested justification of plausibility of these results at clarification but company did not provide

Comparator	Incremental OS RMST	Incremental LY*	% LYG after observed data
Chemotherapy	[redacted]	[redacted]	[redacted]
Pembrolizumab-chemotherapy	[redacted]	[redacted]	[redacted]

Are the results of the modelling plausible?

Abbreviations: LY; Life year, QALY; quality-adjusted life year, LYG; life years gained, OS; overall survival. RMST; restricted mean survival time

Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer

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

NICE National Institute for Health and Care Excellence

Managed access

Company has not made a managed access proposal

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**.

QALY weightings for severity

Company

- QALY shortfall analysis indicates that amivantamab is eligible for a 1.2x severity modifier
- Criteria are met when considering the total discounted QALYs calculated for people in the NCRAS dataset (England-specific RWE)

EAG comments

- No concerns regarding the QALY shortfall analysis, agree that 1.2x severity modifier is appropriate for both company and EAG base cases and regardless of the comparator selected

	QALYs of people without condition (57.8% female, 59.6 years old)	QALYs with the condition on current treatment	**Absolute QALY shortfall (has to be >12)**	**Proportional QALY shortfall (has to be >0.85)**
Company base case	12.58	[redacted]	[redacted]	[redacted]

Is it appropriate to apply a 1.2x severity weighting?

Abbreviations: QALY; quality adjusted life year, NCRAS; national cancer registry and analysis service, RWE; real world evidence

Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer

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

NICE National Institute for Health and Care Excellence

Summary of company and EAG base case assumptions

Differing assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Amivantamab-chemotherapy OS	Weibull distribution	Weibull but with Gompertz scenario
Chemotherapy OS	Gamma distribution	Log logistic
Pembrolizumab-chemotherapy PFS/TTDD (TTNT)	Log-logistic	Log logistic but with Gompertz scenario
Amivantamab TTDD (for amivantamab-chemotherapy)	Weibull	Log-logistic
Chemotherapy TTDD (for amivantamab-chemotherapy)	Weibull	Exponential
Resource use	Implied vial sharing	No vial sharing
AE unit costs	Weighted average including lower grade costs for non-elective short stay	Use of most severe AE unit costs for non-elective short stay

NICE Abbreviations: OS; overall survival, PFS; progression free survival, TTDD; time to treatment discontinuation or death, AE; adverse event

Key issues

Issue	Resolved?	ICER impact
Comparators (scoped comparators and blended comparator)	No	Large
Validity of ITC – adjustment for variables in propensity score weighting	No	Unknown
ITC - lack of sensitivity analyses for base case ATT	No	Unknown
ITC - lack of adjustment for pembrolizumab monotherapy	No	Unknown
Extrapolating longer term effects (TTDD and OS)	No	Large
Treatment effect waning	No	Unknown
Dosing and vial sharing	No	Moderate
Adverse event costs	No	Small
Plausibility of extrapolated benefits	No	Unknown

Other issues

Issue	Resolved?	ICER impact
Squamous histology	No	Unknown
Health state utilities	No	Small
Validation of model	No	Unknown

Abbreviations: ITC; indirect treatment comparison, ATT; average treatment effect for the treated, TTDD; time to treatment discontinuation or death, OS; overall survival, ICER; incremental cost effectiveness ratio

Cost-effectiveness results:

- Cost effectiveness results cannot be reported here because of confidential discounts for included technologies
- Company base case ICER is above £30,000 per QALY gained
- EAG base case ICER is above £30,000 per QALY gained
- All results are presented in Part 2 slides for committee

Abbreviations: ICER; incremental cost effectiveness ratio, QALY; quality adjusted life year

Supplementary appendix

NICE National Institute for Health and Care Excellence

Other issue: Exclusion of squamous histology

ICER Impact: Unknown

Background

- PAPILLON trial excluded people with squamous histology. 99% of trial population was non-squamous/ adenocarcinoma histology type

Company

- State that squamous histology is rare (only 3.05%) and should be removed from the decision problem

EAG comments

- Suggest adapting decision problem to exclude squamous histology or provide additional clinical and cost effectiveness evidence for this population excluded in the key trial

Should squamous histology be considered as part of the decision problem?

ICER Impact: Small

Other issue: Utility values

Background

- Base case uses utilities of [redacted] (progression free) and [redacted] (progressed disease)
- Missing health state utility data for [redacted] in progression free and [redacted] in progressed disease health state

Company

- Proportion of missing data is similar in both trial arms and there is no clear pattern over time in missingness
- Average number with missing data in PF across cycles indicates little impact on overall mean. Do not consider missing data to introduce bias

NSCLC Appraisal	PF Utility	PD utility
ID6328	Redacted	0.678
TA654	0.794	0.678
TA595	Redacted	0.678
TA310	0.78	0.73(3L) 0.46(4L)
TA850	0.713	0.596

Note: for information only, values from EGFR mutation appraisals but not exon20 insertion positive.

EAG comments

- Unclear if data missing at random and extent of impact of missing data on PF PD utilities is uncertain
- Would like to have seen further evidence supporting assumption that data is missing at random
- Scenario using last observation carried forward produced similar cost effectiveness estimates
- Provides scenarios using utility based on TA683 (PF = 0.79, PD = 0.69)

Is the modelling of health state utilities in the PF and PD health states appropriate for decision making?

Abbreviations: HRQoL; health related quality of life, PF; progression free health state, PD; progressed disease health state, EGFR, epidermal growth factor receptor, 3l; third line therapy, 4L; fourth line therapy

Key issue: External Validation

EAG comments

- EAG concerned that the technical verification of the model was insufficient
- company did not provide the TECH-VER checklist despite being asked in the request for clarification.

Company

- Model structure as developed based on global advisory board input
- Model also had stress test and technical validation
- TECH-VER checklist not completed

Is the chosen model validity assessment appropriate?

Reliability of ITC- sensitivity analysis - results

UK only sensitivity analysis results are in broadly in line with base case ITC results

Overall survival (UK data only, considering full NCRAS sample, n=23)

- EAG requested the company to conduct sensitivity analysis with UK only NCRAS data from within NECTAR study dataset
- UK sensitivity analysis results consistent with ATT results

TTNT (UK data only, considering full NCRAS sample, n=23)

Back to Key Issue

Are the results of the ITC appropriate for decision making?

Abbreviations: ITC; indirect treatment comparison, TTNT; time to next treatment, NCRAS, national cancer registry and analysis service, ATT; average treatment effect of the treated, ACP; amivantamab-chemotherapy, ATC; average treatment effect in the control arm, RW; real world

Extrapolations of OS (treatment switching)

Adjustment for subsequent treatments in the chemotherapy arm of PAPILLON

[redacted]

- [redacted] of people in the chemotherapy arm switched to amivantamab monotherapy upon progression.
- Company carried out various methods of treatment switching adjustment
- IPCW used in base case
- EAG considers that treatment-switching adjustment methods used by the company to be appropriate

Back to Key Issue

Method	Median OS (months)	OS HR versus amivantamab - chemotherapy (95% CI)	P-value
PAPILLON trial (ITT)	28.86	[redacted]	0.1825
PAPILLON trial (IPCW)	[redacted]	[redacted]	[redacted]
PAPILLON trial (TSE)	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
RWE (NECTAR study)	[redacted]	[redacted]	[redacted]

Abbreviations: OS; overall survival, CP; carboplatin plus pemetrexed, ITT; intention to treat, IPCW; inverse probability weighting of censoring, TSE; two stage elimination, RWE; real world evidence

Decision problem

Population, intervention, comparators and outcomes from the scope

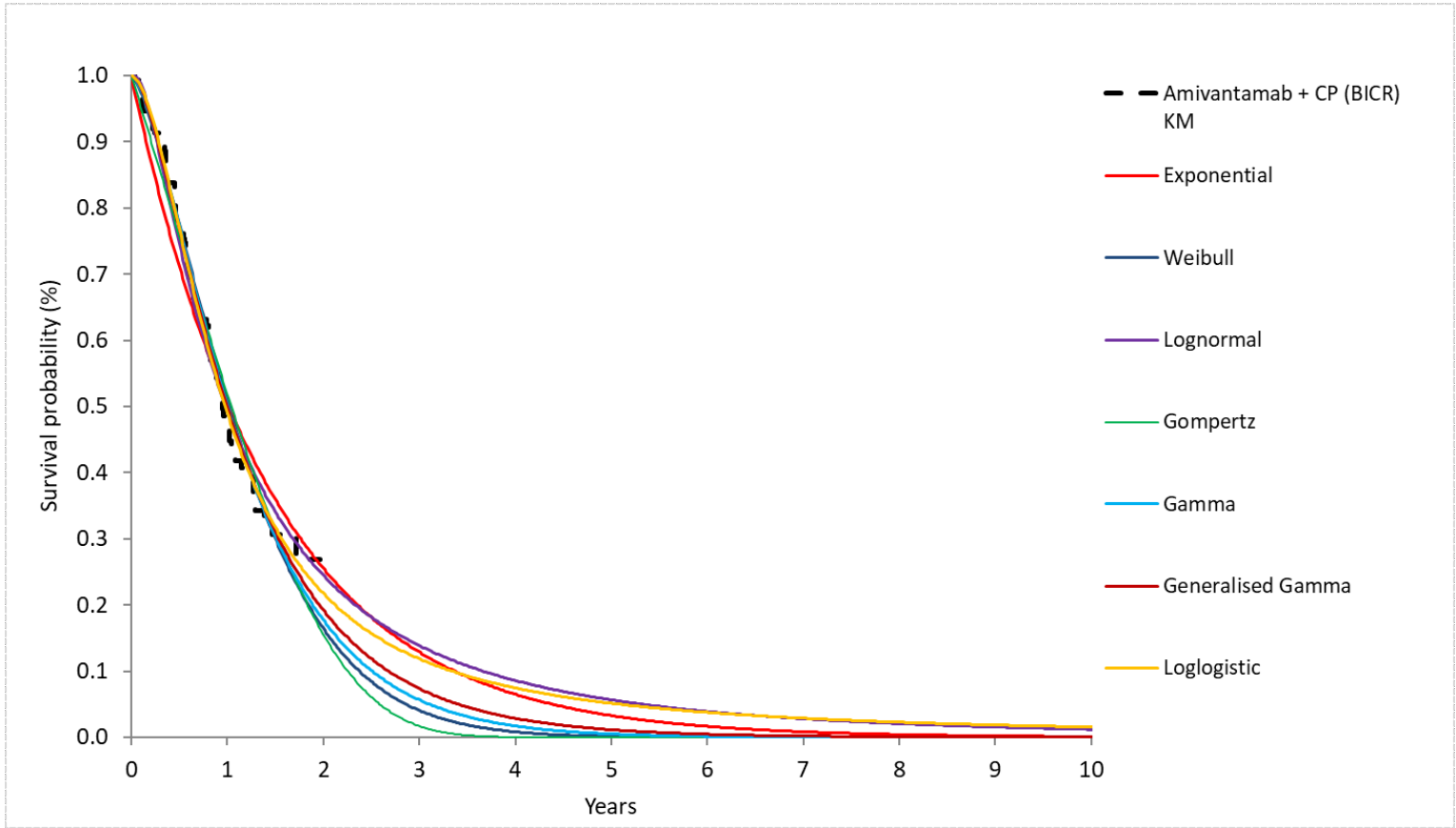
	Final scope	Company	EAG comments
Population	Adults with untreated, locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation	First-line treatment of adult patients with advanced NSCLC with activating EGFR exon 20 insertion mutations	Aligned to the licensed indication for amivantamab, as per the marketing authorisation from the MHRA
Intervention	Amivantamab in combination with carboplatin and pemetrexed.	As per NICE scope.	No comments
Comparators	• Chemotherapy • Pembrolizumab • Atezolizumab • TKIs	• Carboplatin with pemetrexed • Pembrolizumab with carboplatin and pemetrexed • Pembrolizumab monotherapy • UK RWE (collected from the NCRAS dataset) – as scenario.	Company disagree other chemotherapy and atezolizumab are relevant comparators. EGFR TKIs: Exon 20 mutations usually resistant to EGFR TKIs
Outcomes	• OS, PFS, ORR, TTST, AEs, HRQoL	PFS, ORR, DOR, OS, TTST, PFS(post subsequent therapy), TTSP AEs, HRQoL	Outcomes in NICE scope match PAPILLON trial

Abbreviations: AEs, adverse events; HRQoL, health-related quality of life; PFS, progression-free survival; OS, overall survival; RR, response rate, DOR; duration of response, ORR; overall response rate, TTST; time to subsequent treatment, TTSP; time to symptomatic progression, HRQoL; health related quality of life, TKI; tyrosine kinase inhibitor, RWE; real world evidence, EGFR; epidermal growth factor, MHRA; medicines and health regulatory agency

Extrapolations of PFS

TTDD data were used to model costs for amivantamab-chemotherapy

PFS extrapolations for Amivantamab: amivantamab-chemotherapy arm



- **Company:** Log logistic had the best statistical fit to data but tail of >5% remaining progression free after 5 years seen as clinically implausible by experts.
- Company base case uses Gamma distribution
- EAG agree with company approach for

Abbreviations: PFS; progression free survival

Propensity score weighting

Back to Key Issue

Comparison of baseline characteristics within analysis

Baseline characteristics (SLR and clinical experts)	US	NCRAS	ESME	Included in the analysis	Reason for exclusion
Functional status ECOG at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presence of brain metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presence of liver metastases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any other metastatic locations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian ethnicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Smoking history	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SLR; systematic literature review, NCRAS; national cancer registry and analysis service, ECOG; eastern cooperative oncology group (performance status tool)

Estimates of comparator market share

Back to Key Issue

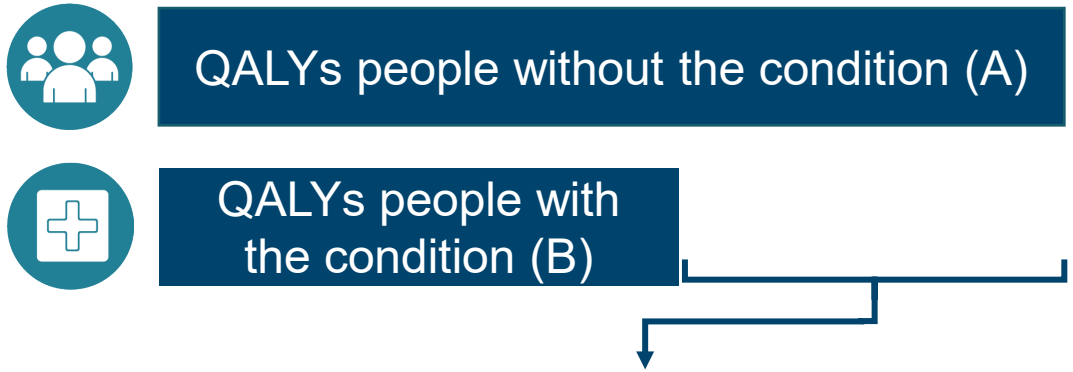
Estimates of current practice for EGFR exon20+ NSCLC vary

Treatment	Company advisory board	EAG clinical expert	EGFR+ patient survey (n=21)
Carboplatin with pemetrexed	70%	60%	70%*
Carboplatin or cisplatin	-	10%	-
Pembrolizumab with platinum chemotherapy	30%	30%	-
Conventional TKIs (mainly osimertinib)	-	-	30%

Abbreviations: SLR; systematic literature review, NCRAS; national cancer registry and analysis service, ECOG; eastern cooperative oncology group (performance status tool)
*Predominantly carboplatin with pemetrexed but carboplatin with vinorelbine or paclitaxel were also cited

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year