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Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer

Technology appraisal committee D [12th June 2025]

Chair: Raju Reddy

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Company: Johnson & Johnson

Amivantamab with lazertinib for untreated EGFR 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 EGFR-positive non-small-cell lung cancer

Epidemiology

- In 2022, 36,886 new lung cancer cases in England of which 80-85% (approx. 29,500-31,300) are NSCLC
- Around 15% (approx. 4,500) of advanced NSCLC cases have EGFR mutations
- Around 90% (approx. 4000) of EGFR mutations are exon 19 deletions or exon 21 L858R mutations, known as common EGFR mutations (cEGFR)
- EGFR mutations: median age of diagnosis 60 years old, more common in females and non-smokers

Symptoms

- Symptoms are non-specific and may be disregarded leading to advanced cancer diagnosis

Prognosis

- In 2022, 66% (approx. 20,000) of NSCLC diagnoses were in advanced stages (3 or 4)
- Estimated 5-year survival for advanced stages was 7.7% from 2016-2020
- Advanced lung cancers frequently metastasise to the central nervous system (brain metastasis)

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer

Patient perspectives

Patients would welcome more treatment options for EGFR positive NSCLC

Submission from Roy Castle Lung Cancer Foundation and EGFR+ UK

- People with EGFR+ NSCLC younger and light/non-smokers compared to the general lung cancer population (can result in delayed diagnosis as don't fit "typical" patient profile)
- Brain metastases (common with EGFR+) mean people lose driving license, significant impact on independence, family and increases caregiver burden.
- Limited lines of treatment available for EGFR+: they only work for a limited time
- Patient questions about sequencing, could you have osimertinib after ami-laz?
- Patient preference is important: interest in ami-laz from many patients but some want to spend as little time as possible in clinical settings

Abbreviations: Ami-laz, amivantamab with lazertinib; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer

Patient perspectives

Patients would welcome more treatment options for EGFR positive NSCLC

Submission from Roy Castle Lung Cancer Foundation and EGFR+ UK

"I was completely shocked and devastated. It's strange… if someone has said I had breast cancer, I'm not sure it would have been so shocking. But as someone who has never smoked, being told I had lung cancer just blind-sided me completely. I just feel so scared and so alone."

*"I would definitely take AmiLaz. I know it looks to be a bit more toxic than Osi and it is a pain to go into hospital sometimes, but if it would buy me more time with my kids (without having to take chemo) I would 100% do it."**

*"If you have Amivantamab and Lazertinib as first line, will you still be able to have Osimertinib afterwards? And will it still work as well?"**

"I am struggling with my diagnosis at the moment. I keep reading that the average time on treatment is about 18 months – what happens next? … …It's so stressful knowing there isn't really anything else to help me."

*"Going to hospital makes me feel like a cancer patient – taking tablets at home almost allows me to forget. Not that you can ever **really** forget."*

Abbreviations: Ami-laz, amivantamab with lazertinib; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer

Clinical perspectives:

Improved disease response but increased burden on patients and cancer centres

Submissions from British Thoracic Oncology Group and Association of Respiratory Nurses:

Benefits of amivantamab [IV] plus lazertinib [Oral tablet] (ami-laz)

- Main aim of treatment is to prolong survival and maintain or improve quality of life
- Improvement in PFS of 3 months or tumour stabilisation/shrinkage would be clinically significant
- High risk patients with brain or liver metastases or high disease burden may particularly benefit
- May offer a chemotherapy free approach, leaving chemotherapy to second line.

Additional burdens of ami-laz

- Associated with increased toxicity, (e.g skin toxicity, risk of VTE) which may require proactive management and may not be suitable for all patients e.g. frailty
- More time in a clinical setting, increased chair time (IV, admin and split first amivantamab dose due to early risk of infusion reactions)
- Possible treatment delays due to day centre waits unlike oral treatments which can start “same day”
- Incoming subcutaneous formulation of amivantamab will likely reduce toxicity and resource issues

Abbreviations: EGFR, epidermal growth factor receptor; IV, intravenous; PFS, progression-free survival; VTE, venous thromboembolism

Equality considerations

Socio-economic, ethnicity, and gender factors may affect outcomes

The company highlighted a number of potential equalities issues:

- The UKLCC (UK Lung Cancer Coalition) reports highlight significant impact of lower socio-economic factors on health inequalities, particularly in relation to lung cancer
- EGFR mutations are more common in women and people with Asian heritage
- Compared with patients of White ethnicity, patients of Asian ethnicity were more likely to be diagnosed with later-stage lung cancer and had a longer median time to treatment initiation
- Stigma is a major concern for lung cancer patients, as it is largely driven by a perception that it is ‘self-inflicted’ due to the public recognising the link between lung cancer and smoking

Abbreviations: EGFR, epidermal growth factor receptor

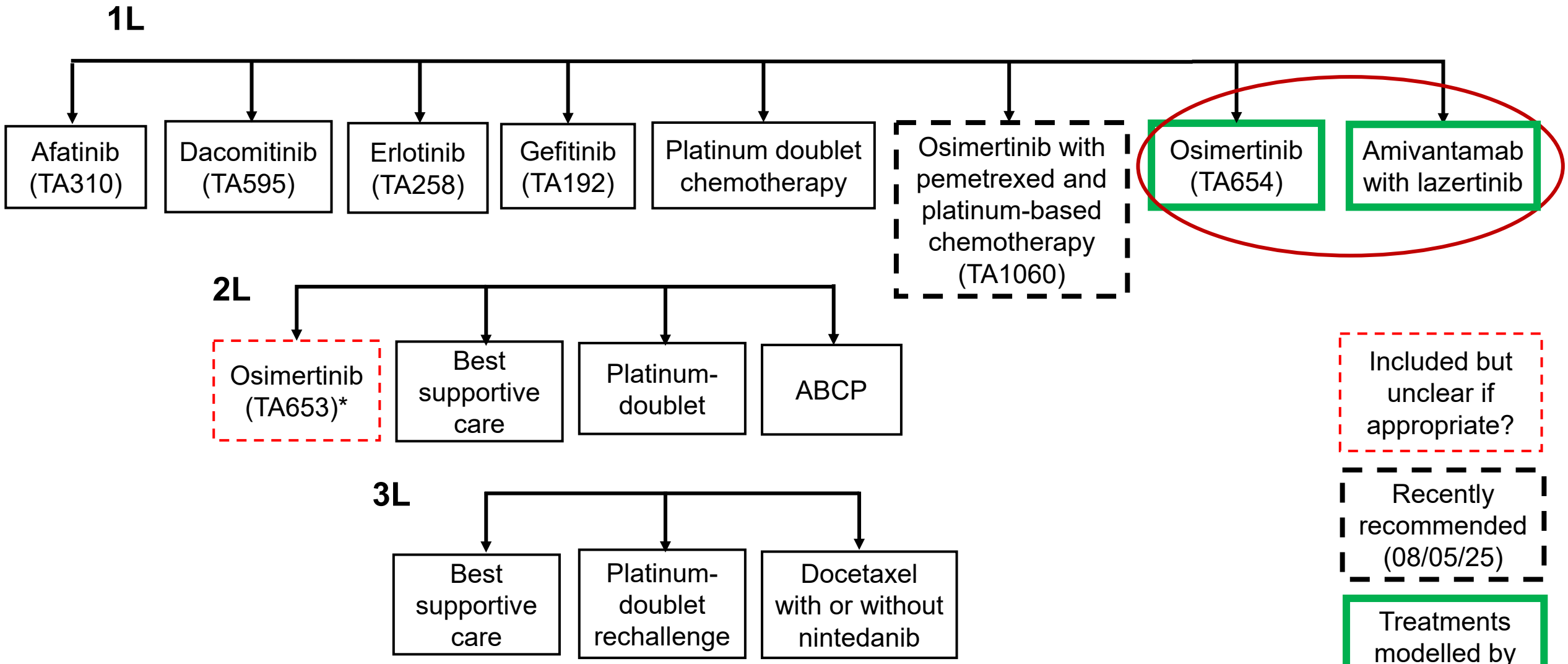
Amivantamab (Rybrevant, Janssen) with lazertinib (Lazcluze, Janssen)

Marketing authorisation	• Amivantamab in combination with lazertinib is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations
Mechanism of action	• Amivantamab is a bispecific antibody binds to both the EGFR and MET receptors • Lazertinib is third-generation EGFR tyrosine kinase inhibitor that selectively inhibits both common EGFR mutations and the EGFR T790M mutation

Administration	• **Amivantamab** (*each vial is 350mg)*
	  • Body weight at baseline <80 kg:
	  • Weeks 1–4: 1,050 mg (3 vials) weekly - week 1 – split infusion on Day 1 and 2, Weeks 2 to 4 – infusion on Day 1 of week
	  • Week 5 onwards: 1,050 mg every 2 weeks
	  • Body weight at baseline ≥80 kg:
	  • Weeks 1–4: 1,400 mg (4 vials) weekly - week 1 – split infusion on Day 1 and 2, weeks 2 to 4 – infusion on Day 1 of week
	  • Week 5 onwards: 1,400 mg every 2 weeks
	• **Lazertinib** *(tablets are either 80mg or 240mg)*
	  • 240 mg once daily

Price	• The list price of amivantamab is £1,079 per 7ml infusion vial (350mg) • The list price for lazertinib 80 mg (56 tablets) is £4,128.50 per pack, and the list price for lazertinib 240 mg (28 tablets) is £6,192.75 per pack. • Amivantamab and lazertinib are subject to a simple PAS discount

Treatment pathway for previously untreated locally advanced or metastatic EGFR-positive NSCLC



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*Would osimertinib (TA653) be given at second line after ami-laz?

Key issues

Key issue	ICER impact
Osimertinib with chemotherapy as a comparator	Unknown
Uncertainty around modelling of TTD	Small
Administration costs for amivantamab	Large
Utilities for the progression-free health state	Moderate

Other issue	ICER impact
Uncertainty in the long-term predictions for OS	Large
Resource use - Resolved	Small
Adverse events - Resolved	Small

Abbreviations: OS, overall survival; TTD, time to treatment discontinuation

Key issues: Osimertinib with chemotherapy as a comparator

Unknown

EAG notes company did not present a comparison against osimertinib with chemotherapy

Background

- At point of CS, osimertinib with chemotherapy had not been recommended in this population. It was included on the final scope "subject to NICE appraisal"
- Osimertinib with chemotherapy was recommended in May 2025

Company

- At the time of submission, osimertinib with chemotherapy was not recommended by NICE and experts advised it did not represent an established treatment option in clinical practice in the NHS in England
- UK data from NCRAS showed 90.5% with similar characteristics to MARIPOSA trial received osi mono at 1L
- Both osimertinib with chemo and ami-laz have been compared with osimertinib mono
- NICE manual states that relevant comparators should be treatments that are established NHS practice

EAG comments

- The EAG would have preferred that comparison with osimertinib with chemotherapy was available
- At time of CS, clinical advice to the EAG was that osimertinib with chemotherapy was not used in clinical practice

CDF Lead

- In May 2025 (the first full month of osimertinib with chemotherapy usage) 23% of osi usage was with chemo
- June 2025 usage figures are expected to be higher

What are the relevant comparators for this appraisal?

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer

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Key clinical trials

Clinical trial designs and outcomes

For a diagram of the study design, see appendix

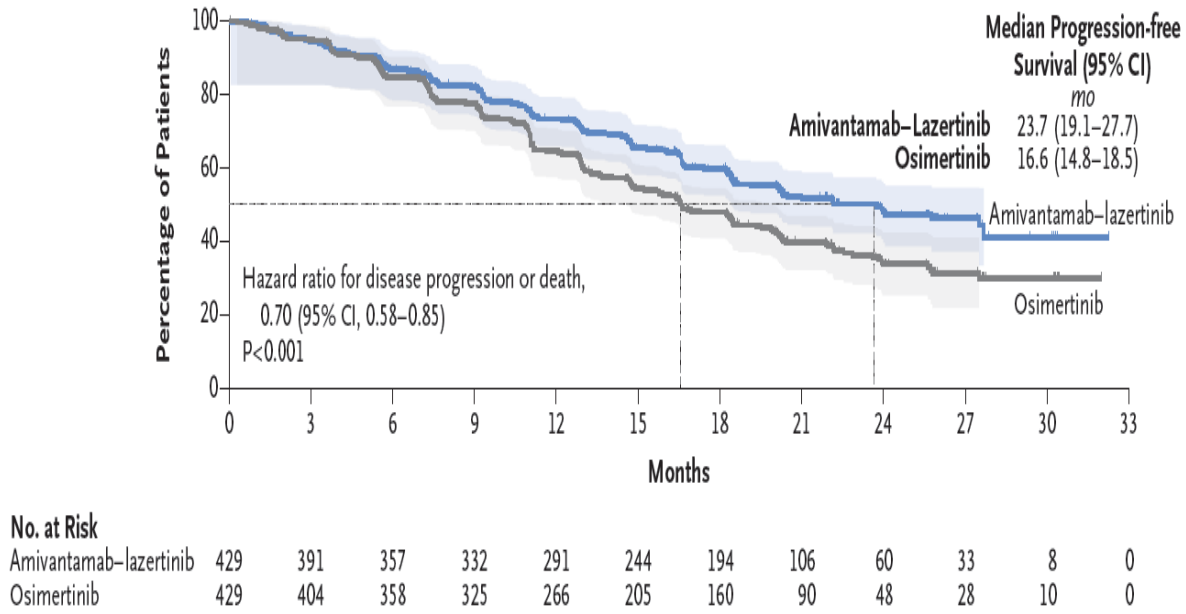
	MARIPOSA
Design	Phase 3 Randomised
Population	People with untreated cEGFRm advanced NSCLC
Intervention	Amivantamab with lazertinib (open label)
Comparator	Osimertinib in combination with placebo (double blind) Lazertinib in combination with placebo (double blind) – (Not used in model)
Key outcomes	PFS (primary), OS, ORR, DOR, PFS2, TTSP, EORTC-QLQ-C30, EQ-5D-5L
Locations	267 sites across 28 countries, including 7 UK sites
Subgroups	Age, Sex, Race, Weight, Baseline ECOG PS, history of smoking, history of brain metastasis, EFGR mutation

Characteristic	Ami-laz (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	64 (25, 88)	63 (28, 88)	63 (31, 87)
Sex, n (%)			
Female	275 (64)	251 (59)	136 (63)
Race, n (%)			
Asian	250 (58)	251 (59)	128 (59)
White	164 (38)	165 (38)	79 (37)
Other	15 (4)	13 (3)	9 (4)

Key clinical trial results – MARIPOSA

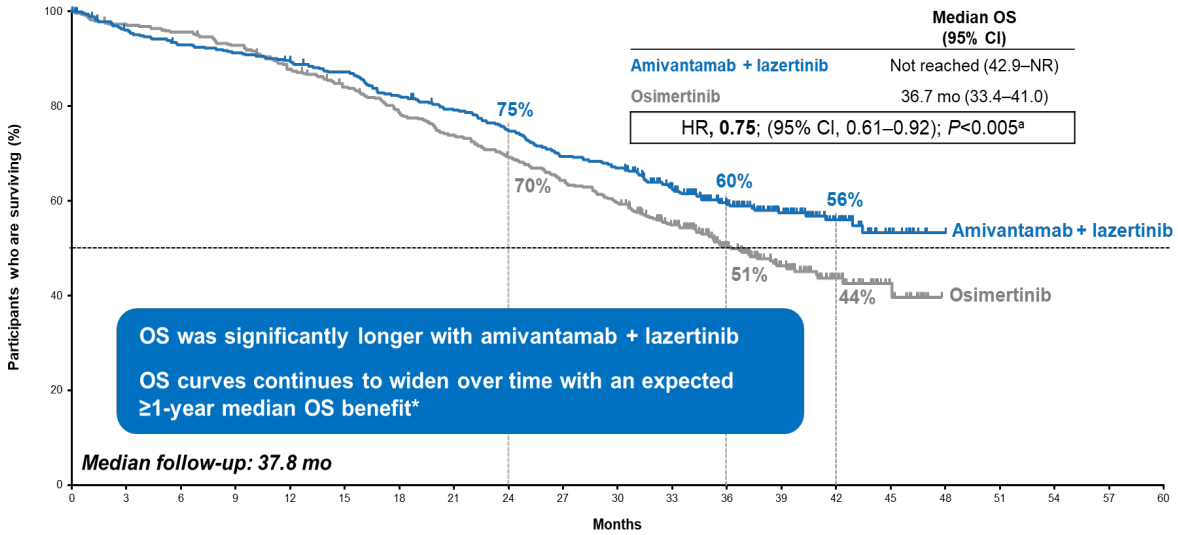
Amivantamab with lazertinib improves OS and PFS over osimertinib

Figure: Amivantamab with lazertinib vs. osimertinib – PFS
August 2023 DCO



HR (95% CI; p-value)	0.70 (0.58, 0.85) p<0.001

Figure: Amivantamab with lazertinib vs. osimertinib – OS
December 2024 DCO



*Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is predicted to exceed 1 year.

Note: Last participant was enrolled in May 2022. Clinical cutoff date was December 4, 2024. In total, 390 deaths had occurred in the amivantamab + lazertinib (173 deaths) and osimertinib (217 deaths) arms.

[a]P-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model.

HR (95% CI; p-value)	0.75 (0.61-0.92) p<0.005

Note: PFS was not updated in December 2024 DCO - August 2023 DCO is the most recent PFS data available

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Why was PFS not available in the latest data cut?

Key clinical trial results – MARIPOSA

Amivantamab with lazertinib improves PFS2 over Osimertinib

Figure: Amivantamab with lazertinib vs. osimertinib – PFS2
December 2024 DCO

Figure: Amivantamab with lazertinib vs. osimertinib – TTD
December 2024 DCO

HR (95% CI; nominal p-value)	[redacted]

Click to see adverse events from MARIPOSA

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Would amivantamab and lazertinib be stopped separately in clinical practice?

Key issues: Uncertainty around modelling of TTD

Small

Company use exponential extrapolation to model TTD, EAG prefer using splines

Background

- The company fit individual TTD curves for amivantamab, lazertinib, and for osimertinib monotherapy
- The company selected the exponential distribution for all 3 TTD curves in its base case
- The company provided updated TTD data from the December 2024 DCO and maintained its preference for exponential distributions for each component

Company

- The longer-term data from the December 2024 DCO mitigates uncertainty raised by the EAG
- TTD curves from the December 2024 DCO have been validated with a key clinician from the UK

Amivantamab (exponential)

- Exponential curve has strong statistical and visual fit and close alignment with clinical timepoint estimates
- Clinician advised that exponential and gamma were most appropriate extrapolations

Lazertinib (exponential)

- Exponential curve has strong statistical and visual fit and close alignment with clinical timepoint estimates
- Clinician advised that gamma, Generalised gamma, or Weibull were most appropriate extrapolations – exponential distribution closely aligned with the characteristics of that selection

Osimertinib (exponential)

- Exponential curve has strong visual fit and close alignment with clinical timepoint estimates
- Clinician advised that exponential and loglogistic were most appropriate extrapolations – loglogistic presents a more optimistic and higher TTD for osimertinib compared to base case

Abbreviations: DCO, data cut off; TTD, time to treatment discontinuation

Key issues: Uncertainty around modelling of TTD

Small

Company use exponential extrapolation to model TTD, EAG prefer using splines

EAG comments

- Fitting separate models is a reasonable approach. But EAG prefer different distributions.

Amivantamab (2-knot normal spline)

- Exponential curve predicts a constant hazard while smoothed empirical hazard plot appears to fluctuate
- All splines fit KM well and provide a better fit to the empirical hazard function
- 2-knot normal spline chosen because of good statistical fit, good predictions to the hazard function, as well as closer predictions to clinicians' estimates of 8-year TTD

Lazertinib (1-knot hazards spline)

- Exponential curve predicts a constant hazard while smoothed empirical hazard plot appears to fluctuate
- All splines fit KM well and 1- and 2-knot models provide a better fit to the empirical hazard function
- 1-knot hazards chosen because it captures hazard shape well, provides good statistical fit to KM data and produces reasonable predictions

Osimertinib (1-knot normal spline)

- Exponential provides close alignment with expert estimations but has poor statistical fit to data – AIC 13 points higher than gamma
- Gamma, Weibull, generalised gamma and all spline models provide good alignment with observed hazards
- 1-knot normal spline chosen because it provides close estimation to clinicians' 8-year estimates, good statistical fit and reasonable hazard shape

Abbreviations: DCO, data cut off; KM, Kaplan-Meier; TTD, time to treatment discontinuation

Key issues: Uncertainty around modelling of TTD

Small

Company use exponential extrapolation to model TTD, EAG prefer using splines

Amivantamab – company clinician estimates and predicted TTD

Year	Company clinicians' mean estimates	Exponential (company BC)	2-knot normal (EAG BC)
4	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]

Lazertinib – company clinician estimates and predicted TTD

Year	Company clinicians' mean estimates	Exponential (company BC)	1-knot hazards (EAG BC)	2-knot normal (EAG scenario)
4	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]

Osimertinib – company clinician estimates and predicted TTD

Year	Company clinicians' mean estimates	Exponential (company BC)	1-knot normal (EAG BC)	2-knot normal (EAG scenario)
4	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]

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What are the most appropriate TTD extrapolations to use for each treatment?

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer

- ❑ Background and key issues
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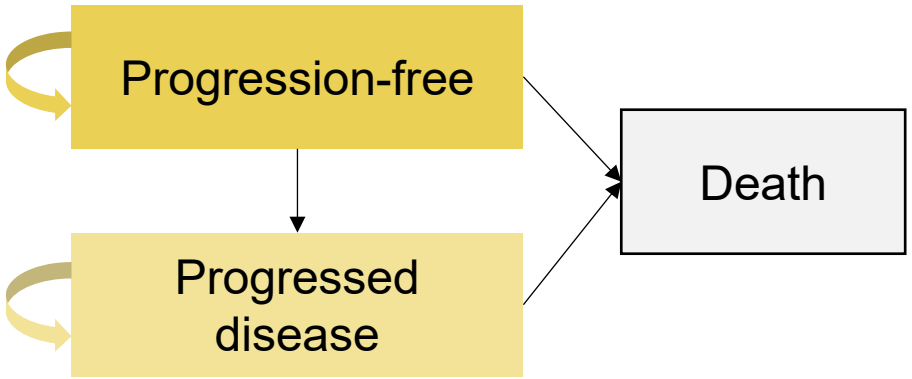
Company's model overview

Company developed a three-state partitioned survival model

Model structure



- Technology affects **costs** by:
  - Treatment acquisition and administration costs
  - Time in more expensive health states
- Technology affects **QALYs** by:
  - Increasing time until progressed disease
  - Increasing OS
- Assumptions with greatest ICER effect:
  - OS extrapolation
  - Administration costs
  - TTD distribution

EAG comments

- PSM aligns with previous appraisals of TKIs including TA595, TA654, and TA1060 which previous committees considered appropriate
- Corrected errors in the company model for EAG base case- see slide

Abbreviations: PSM, partitioned survival model; OS, overall survival; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation

Key issues: Administration costs for amivantamab

Large

EAG concerned that administration costs for amivantamab in the model may be underestimated

Background

- Company applied HRG code SB12Z for the reference cost of administration of amivantamab
- SB12Z is for "delivering simple chemotherapy" including 30 minutes nurse time and 30-60 minutes chair time
- Company also excluded additional costs in the first week for splitting the first dose over two days

Company

- SB12Z is the most appropriate code to use and closely reflects expected clinical practice
- For cycle 3 onwards in PALOMA-3, median infusion duration of 2.25 hours was reported, applying SB12Z is considered reflective of the average infusion time for amivantamab
- SB15Z refers to subsequent elements of a chemotherapy cycle. Whilst amivantamab is administered in a split dose in cycle 1, this refers to a single dose only. So, SB15Z is considered inappropriate

EAG comments

- None of the information provided by the company supports a chair time of less than 60 minutes
- SmPC for amivantamab gives infusion rate of 125 mL/hr from week 4 onwards - requires minimum of 2 hours to administer recommended 250 mL infusion volume
- Prefers to apply SB14Z which allows for over 2 hours of chair time
- 1st amivantamab dose is split so HRG code SB15Z should apply to the second part of the dose as a one-off cost
- Uncertainty about whether to use outpatient or day case costs and NHS reference or payment scheme costs.

Abbreviations: HRG, Healthcare Resource Group

Key issues: Administration costs for amivantamab

Large

EAG concerned that administration costs for amivantamab in the model may be underestimated

CDF Lead

- Amivantamab was associated with a significant number of infusion related reactions (63% of patients had infusion reactions in the MARIPOSA trial) which results in extra monitoring and routine use of premedication, adding chair time of up to 1 hour, particularly for the first few amivantamab administrations.
- The infusion times and the most relevant HRG codes are:
  - Cycle 1 Day 1 (Week 1) 4 hours for amivantamab plus a preceding 1 hour for premedication - **SB14Z**
  - Cycle 1 Day 2 (Week 1) 4 hours for amivantamab plus a preceding 1 hour for premedication - **SB15Z**
  - Cycle 1 Day 8 (Week 2) 3 hours for amivantamab - **SB15Z**
  - Cycle 2 Day 1 (Week 3) 2 or 3 hours for amivantamab depending on patient weight – **SB13Z** or **SB14Z** but **SB14Z** preferred due to the risk of infusion reactions in the early treatment cycles
  - Cycle 2 Day 8 (Week 4) D1 2 hours of amivantamab - **SB15Z**
  - Cycle 3 Day 1 (Week 5) D1 2 hours of amivantamab - **SB13Z**
  - Each subsequent 2-weekly cycle - **SB13Z**
  - If lazertinib is continued as monotherapy after amivantamab is stopped because of toxicity, lazertinib would be dispensed in 4 weekly cycles, using HRG code for oral administration - **SB11Z**

Abbreviations: HRG, Healthcare Resource Group

Key issues: Administration costs for amivantamab

Large

EAG concerned that administration costs for amivantamab in the model may be underestimated

Table - Chemotherapy delivery HRGs

HRG code	Definition	Explanation	NHS Reference cost	NHS Payment scheme
SB12Z	Deliver simple parenteral chemotherapy	Overall time of 30min nurse time and 30 to 60min chair time for the delivery of a complete cycle.	OP: £133 DC: £418	£182
SB13Z	Deliver more complex parenteral chemotherapy	Overall time of 60min nurse time and up to 120 min chair time for the delivery of a complete cycle.	OP: £184 DC: £528	£365
SB14Z	Deliver complex chemotherapy, including prolonged infusional treatment	Overall time of 60min nurse time and over two hours chair time for the delivery of a complete cycle.	OP: £337 DC: £570	£547
SB15Z	Deliver subsequent elements of a chemotherapy cycle	Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance, for example day 8 of a day 1 and 8 regimen	OP: £198 DC: £426	£365
SB17Z	Deliver chemotherapy for regimens not on the National List	Delivering chemotherapy regimens not included on the National List. All prices negotiated locally.	OP: £287 DC: £496	N/A

What are the most appropriate costs to apply for the administration of amivantamab?

Which HRG code?

Outpatient or day-case?

Reference cost or payment scheme?

Key issues: Utilities for the progression-free health state

Moderate

Table: Approaches to estimate utility in the PF health state

	Approach 1: multiple MMRM without the treatment term – used in the CS	Approach 2: a single MMRM, all patients (adjusted by the progression status)	Approach 3: a single MMRM, progression - free patients only (EAG base case)
Amivantamab with lazertinib	[redacted]	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]	[redacted]

Table: Base case HSUVs

	Company		EAG	
	Ami-laz	Osi	Ami-laz	Osi
Progression-free	[redacted]		[redacted]	[redacted]
Progressed disease	[redacted]		[redacted]	[redacted]

Which utilities should be used to inform the model?

Abbreviations: AE, adverse events; ami-laz, amivantamab with lazertinib; CI, confidence interval; EFGR, epithelial growth factor receptor; EQ-5D-3L, EURO-QOL 5 dimensions 3 levels; NSCLC, non-small-cell lung cancer; osi, osimertinib; PFS, progression-free survival; HSUV, health state utility values

Key issues: Utilities for the progression-free health state

Moderate

Utilities from MARIPOSA trial: EAG prefers treatment-specific utilities for the progression-free health state

Background

- Company's base case uses treatment-independent utilities for PFS health state, pooled from all PFS patients from the mean utility across 18 different points in the trial

Company

- In cycle analysis the mean utility values for each arm are close in value at each point - many overlap 95% CIs
- Inappropriate to use treatment-specific utility for PFS because osimertinib PFS values [redacted] higher than:
  - the expected general population utility value noted in TA1060 (age 55–64 years: 0.799 [Kind et al. 1999]),
  - the pooled value currently used in both arms of the model [redacted] and
  - the previously accepted value in advanced EGFR-mutated NSCLC appraisals (0.794 [TA654 and TA1060]).

EAG comments

- When accounting for AEs already captured separately in the model, regression analysis shows a significant difference in utilities between arms. In cycle analysis [redacted]
- UK population EQ-5D-3L (62.3 years) is 0.826 (Hernández Alava et al. 2022) so [redacted] for PFS is plausible
- TA654 and TA1060 value (0.794) was from pooled FLAURA data - PFS utility in the osimertinib arm was 0.803

Which utilities should be used to inform the model?

Abbreviations: AE, adverse events; ami-laz, amivantamab with lazertinib; CI, confidence interval; EFGR, epithelial growth factor receptor; EQ-5D-3L, EURO-QOL 5 dimensions 3 levels; NSCLC, non-small-cell lung cancer; osi, osimertinib; PFS, progression-free survival; HSUV, health state utility values

Other issues: Uncertainty in the long-term predictions for OS

Large

EAG use company preferred extrapolations in their base case but explore other plausible models in scenarios

Company

- The longer-term data from the December 2024 DCO mitigates uncertainty raised by the EAG

Ami-laz

- Weibull curve has strong statistical and visual fit, and close alignment with clinical timepoint estimates
- 10-year expert survival estimation for the Weibull extrapolation is [redacted] which is closer to the mean of the estimates provided by clinicians [redacted] than the 1-knot hazard extrapolation is [redacted]

Osimertinib

- Weibull curve has strong statistical and visual fit, and close alignment with clinical timepoint estimates
- OS curves were validated with Weibull and Gamma considered most appropriate for long-term osimertinib OS

EAG comments

Ami-laz

- Weibull most appropriate parametric model – 1 and 2-knot hazard splines also appropriate but neither Weibull or the spline model provide great representation of hazard function
- Use Weibull distribution in base-case but explore impact of 1-knot hazard as plausible alternative scenario

Osimertinib

- Parametric models are adequate for fitting osimertinib OS
- Weibull and gamma appropriate: good statistical fit, reasonable hazard shape and close to clinicians' estimates
- Use Weibull in base-case but explore impact of gamma model as a plausible alternative scenario

Abbreviations: Ami-laz, amivantamab with lazertinib; DCO, data cut off; OS, overall survival

Other issues: Uncertainty in the long-term predictions for OS

Large

Life years	Base cases	EAG scenario
Ami-laz	5.21	4.79
Osi	3.68	3.96
Δ LY	1.54	0.83

Ami-laz: OS estimates

Year	Company experts mean	Weibull	1-knot hazard
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]

Osimertinib: OS estimates

Year	Company experts mean	Weibull	Gamma
5	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]

Which distributions should be used to extrapolate OS for each arm?

Summary of company and EAG base case assumption differences

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Amivantamab TTD curve	Exponential	2-knot normal
Lazertinib TTD curve	Exponential	1-knot hazards
Osimertinib TTD curve	Exponential	1-knot normal
PFS utilities	Pooled utility: [redacted] for both arms	Treatment specific utility: Ami-laz: [redacted] Osimertinib monotherapy: [redacted]
Amivantamab administration costs	HRG code SB12Z used for all doses of amivantamab including 1st dose	HRG code SB14Z used for most amivantamab doses - SB15Z used for second half of 1st dose
Resource use frequencies	Company accept EAG assumptions: TA1060 values only	
Adverse events	Company accept EAG assumptions: Include all grade ≥3 VTEs Include admission costs for all VTEs and diagnosis costs for grade ≥3 PEs	

Abbreviations:

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

PAS discounts

When the company and EAG base case ICERs are calculated using confidential prices:

Company base case is below £30,000 per QALY gained
EAG base case is above £30,000 per QALY gained

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer

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- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

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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**.

Company has not submitted a proposal for managed access

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer

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

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Key issues

Key issue	ICER impact
Osimertinib with chemotherapy as a comparator	Unknown
Uncertainty around modelling of TTD	Small
Administration costs for amivantamab	Large
Utilities for the progression-free health state	Moderate

Other issue	ICER impact
Uncertainty in the long-term predictions for OS	Large
Resource use - Resolved	Small
Adverse events - Resolved	Small

Abbreviations: OS, overall survival; TTD, time to treatment discontinuation

Decision making framework – Issues to discuss

What are committee's preferred assumptions?	
Osimertinib with chemotherapy as a comparator	Is osimertinib with chemotherapy a suitable comparator for this appraisal?
TTD extrapolations	What are the most appropriate TTD extrapolations to use for each component?
Amivantamab administration costs	What are the most appropriate costs to apply for the administration of amivantamab?
Treatment specific utilities	Should treatment-specific utilities be used in the model?
Resource use	Should the resource use figures from TA1060 be used in the model?
Adverse events	Should all grade ≥ 3 VTEs be included in the model? Should admission and diagnosis costs be included?
OS extrapolations	What are the most appropriate OS extrapolations to use for each treatment arm?
What is the committee's preferred ICER?	What is the committee's preferred ICER threshold - and why? What is the committee's preferred ICER (is this a range)?

Abbreviations: OS, overall survival; TTD, time to treatment discontinuation; VTE, venous-thrombus event

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer

Supplementary appendix

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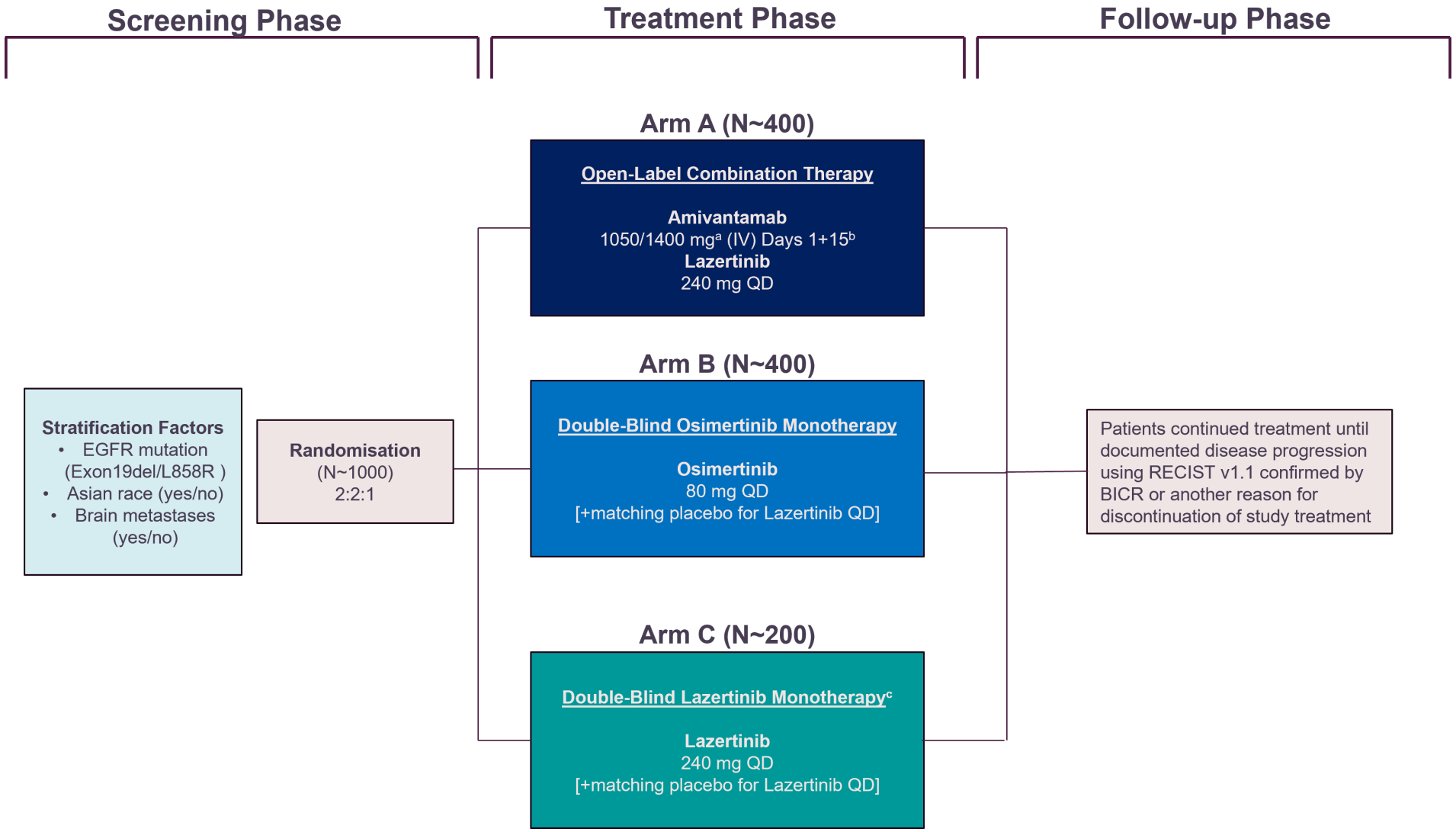
Key clinical trials

Clinical trial designs and outcomes



Company's model overview

Company developed a three-state partitioned survival model

EAG comments

- Errors corrected include:
  - Unit costs that the EAG derived from the 2023/24 National Schedule of NHS Costs were used
  - For the management of VTE, it was assumed that rivaroxaban would be administered for 154 days, which aligned with the duration of VTE observed in the MARIPOSA trial
  - The dose of dexamethasone was changed from 60 mg to 30 mg during the first treatment cycle
  - Enoxaparin sodium is scheduled to be administered for 17 weeks
  - The cost of IRRs was adjusted for inflation to 2022/23 values using the NHSCII (pay and prices)
  - The duration of 'IO ± chemotherapy ± VEGFi' in second-line treatment was revised to 10.3 months, instead of 8.3 months
  - The incidence of fatigue for 'IO ± chemotherapy ± VEGFi' was revised to 3.3%, based on a sample size of 13 out of 393 patients

Other issues: Resource use

Small (reduction)

EAG prefers to use resource use figures from TA1060

Background

- In the original company submission, the types and frequencies of resources were based on previous HTA submissions (TA531, referred to by TA584)
- Resource use estimates in TA531 were based on Brown et al. (2013)
- Brown et al. referred to Maslove et al. (2005), NICE Guideline CG121 (2009) and the Marie Curie report (2004)
- The EAG were unable to find the original values from the Marie Curie report and could not retrieve NICE Guideline CG121 because it had been replaced by NG121
- At clarification, the company updated some resource use figures to match TA1060 (osimertinib with chemotherapy for treating EFGR-positive non-small-cell lung cancer) which referenced Brown et al. but revised the figures based on advice from clinical experts

EAG comments

- To ensure consistency with recent appraisals, the EAG prefers to use TA1060 as the basis for all resource use figures

Company

- Accepts EAG position, incorporates TA1060 resource use in base case

Should the resource use figures from TA1060 be used in the model?

Other issues: Resource use

Small (reduction)

EAG prefers to use resource use figures from TA1060

Table – resource use figures from TA1060 and company submissions

	Company's original submission		TA1060 committee preferred		Company's model submitted with the clarification response	
	PF	PD	PF	PD	PF	PD
Resource use per year						
Oncology outpatient visit	9.61	7.91	9.61	7.91	9.61	7.91
Chest radiography	6.79	6.50	-	-	-	-
MRI scans	-	-	2	2	2	2
CT scan (chest)	0.62	0.24	2	2	2	2
CT scan (other)	0.36	0.42	2	2	2	2
ECG	1.04	0.88	2	0	1.04	2
Community nurse home visit (20 mins)	8.7	8.7	-	-	8.7	8.7
Clinical nurse specialist	12.0	12.0	12	12	12	12
GP surgery visit	12.0	-	-	-	12.0	-
GP home visit	-	26.09	-	-	-	26.09
Therapist visit	-	26.09	-	-	-	26.09
Annual cost by health state (£)	4,980.06	6,605.17	4,074.88	3,394.07	5,154.74	7,043.16

Should the resource use figures from TA1060 be used in the model?

Other issues: Adverse events

Small

EAG prefer to include all grade ≥ 3 VTEs

Background

- The company included grade 3 or higher TEAEs if they occurred in ≥5% in one of the arms
- Grade ≤2 VTEs were also included because the company considered they were a clinically relevant consideration for amivantamab treatment
- VTEs can include PEs or DVTs – for grade ≥3 AEs, only PEs were included
- The company did not include admission costs for any VTEs or diagnosis costs for grade ≥3 PEs

Company

- In the trial, only [redacted] patients in the amivantamab-lazertinib arm ([redacted]) and [redacted] patients in the osimertinib arm ([redacted]) experienced grade ≥3 DVTs, so these events did not pass the threshold for inclusion
- Management of PE was costed using a weighted average of HRG codes DZ09J–DZ09Q (non-elective short stay) using the weighted average of all PE-related HRG codes is the most appropriate costing approach
- Accepts EAGs position and includes in base case

EAG comments

- Inconsistent to include all grade ≤2 VTEs but only include grade ≥3 PEs – prefer to include all grade ≥3 VTEs
- Costs for managing VTEs were also re-estimated to account for outpatient drug costs for grade ≥ 3 VTE, diagnostic costs for all and emergency department costs for grade ≤ 2 VTE

Should all grade ≥ 3 VTEs be included in the model?
Should admission and diagnosis costs be included?

Abbreviations

Other issues: Adverse events

Small

EAG prefer to include all grade ≥ 3 VTEs

Table – EAGs preferred adverse event costs

Resource use category	DVT	PE	DVT	PE
	Grade ≤ 2	Grade ≤ 2	Grade ≥ 3	Grade ≥ 3
Anticoagulant treatment for 3 to 6 months ([redacted] days rivaroxaban)	£277	£277	£277	£277
Leg vein ultrasound (RD40Z)	£65	NA	£65	NA
Diagnostic scan for PE - CTPA (RD21A)	NA	£114	NA	£114
Emergency department attendance without admission (VB05Z)	£511	£511	NA	NA
Short stay admission for PE	NA	NA	NA	£664
Short stay admission for DVT (YQ51A to YQ51E)	NA	NA	£477	NA
Average cost by VTE category and grade	£853	£902	£819	£1055
Distribution of DVT and PE	55%	45%	23%	77%
Average cost for VTE by grade	£875		£1002	

Adverse events from the MARIPOSA trial

Back to TTD graph

Ami-laz generally has a worse AE profile than osimertinib

Event, n (%)	Amivantamab - lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more AEs	421 (100)	425 (99)
Skin and subcutaneous tissue disorders		
Rash	260 (62)	131 (31)
Dermatitis acneiform	122 (29)	55 (13)
Dry skin	67 (16)	60 (14)
Pruritus	99 (24)	73 (17)
Peripheral oedema	150 (36)	24 (6)
Stomatitis	122 (29)	90 (21)
Gastrointestinal disorders		
Constipation	123 (29)	55 (13)
Nausea	90 (21)	58 (14)
Diarrhoea	123 (29)	190 (44)
Infections and infestations		
Paronychia	288 (68)	121 (28)
COVID-19	111 (26)	103 (24)
Metabolism and nutrition disorders		
Hypoalbuminaemia	204 (48)	26 (6)
Decreased appetite	103 (24)	76 (18)
Hypocalcaemia	88 (21)	35 (8)

Event, n (%)	Amivantamab - lazertinib (N=421)	Osimertinib (N=428)
Blood and lymphatic system disorders		
Anaemia	96 (23)	91 (21)
Leukopenia	26 (6)	66 (15)
Thrombocytopenia	66 (16)	84 (20)
General disorders and administration site conditions		
Asthenia	78 (19)	46 (11)
Fatigue	70 (17)	42 (10)
Muscle spasms	70 (17)	32 (7)
Pain in extremity	64 (15)	22 (5)
Investigations		
Alanine aminotransferase increased	152 (36)	57 (13)
Aspartate aminotransferase increased	121 (29)	58 (14)
Respiratory, thoracic and mediastinal disorders		
Cough	65 (15)	88 (21)
Dyspnoea	51 (12)	68 (16)
Pulmonary embolism	73 (17)	20 (5)

All grade adverse reactions for amivantamab plus lazertinib

22% of people discontinued ami-laz due to adverse reactions

Adverse events of any grade	Proportion
Rash	89%
Nail toxicity	71%
Infusion related reactions	63%
Hyoalbuminaemia	48%
Oedema	47%
Stomatitis	43%
Venous thromboembolism	36%
Alanine aminotransferase increased	36%
Fatigue	32%

Figures extracted from Rybrevant SPC Table 9. Only the most common 10 shown see SPC for details

AE leading to discontinuation	Proportion
Rash	5.5%
Infusion related reactions	4.5%
Nail toxicity	3.6%
Interstitial lung disease	2.9%
Venous thromboembolism	2.9%

Figures extracted from Rybrevant SPC

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Abbreviations: SPC, summary of product characteristics