Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation

For public – contains redacted information

HST committee [20th November 2025]

Chair: Paul Arundel

Lead team: Natalia Kunst, Dusko Ilic, Jonathan Ives

External assessment group: Liverpool Reviews & Implementation Group (LRiG)

Technical team: Giacomo De Guisa, Claire Hawksworth, Richard Diaz

Company: AstraZeneca

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation

- ✓ **Background**
- ❑ Clinical effectiveness and key issues
- ❑ Modelling and cost effectiveness
- ❑ Cost effectiveness results

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Background on EGFRm-positive locally advanced unresectable NSCLC

Causes and epidemiology

- Lung cancer = 3rd most common UK cancer (~49,200 new cases/year) and leading cause of cancer death
- Non-small cell lung cancer (NSCLC) accounts for ~80–85% of lung cancers; adenocarcinoma most common NSCLC subtype
- ~10% of NSCLC cases are driven by EGFR mutations (EGFRm), which are more common in non-smokers and Asian patients

Prognosis and impact

- People with unresectable EGFRm-positive NSCLC face a high risk of progression after CRT, with limited current treatment options and increased physical, emotional and psychological burden from disease surveillance and uncertainty
- Survival after progression is poor; treatment aims to delay disease progression and maintain quality of life
- Current treatments in the NHS comprises of active monitoring and symptom control (best supportive care)

Definitions

- **Locally advanced** is cancer that has spread into tissues around the lungs and might have spread into nearby lymph nodes
- **Unresectable** means inoperable (the cancer cannot be removed by surgery)

Abbreviations: CRT, chemoradiation; EGFRm, epidermal growth factor receptor mutation

Equality considerations

Some potential equalities issues identified at scoping

Scoping consultation and patient organisation submissions

- Geographical variation → leading to inconsistency and inequity in access to care
  - Variation in post-CRT care across centres
  - Differences in access to EGFR testing
- Ethnicity and sex
  - EGFR mutations are more common in women
  - EGFR mutations more prevalent in people of East Asian and some minority ethnic backgrounds, including people of Bangladeshi, Indian, or Pakistani ethnicity
- Minority ethnic groups may be less likely to engage with healthcare systems, highlighting the need for accessible, culturally tailored information

Company submission – No equality issues identified

EAG Report – No equality issues identified

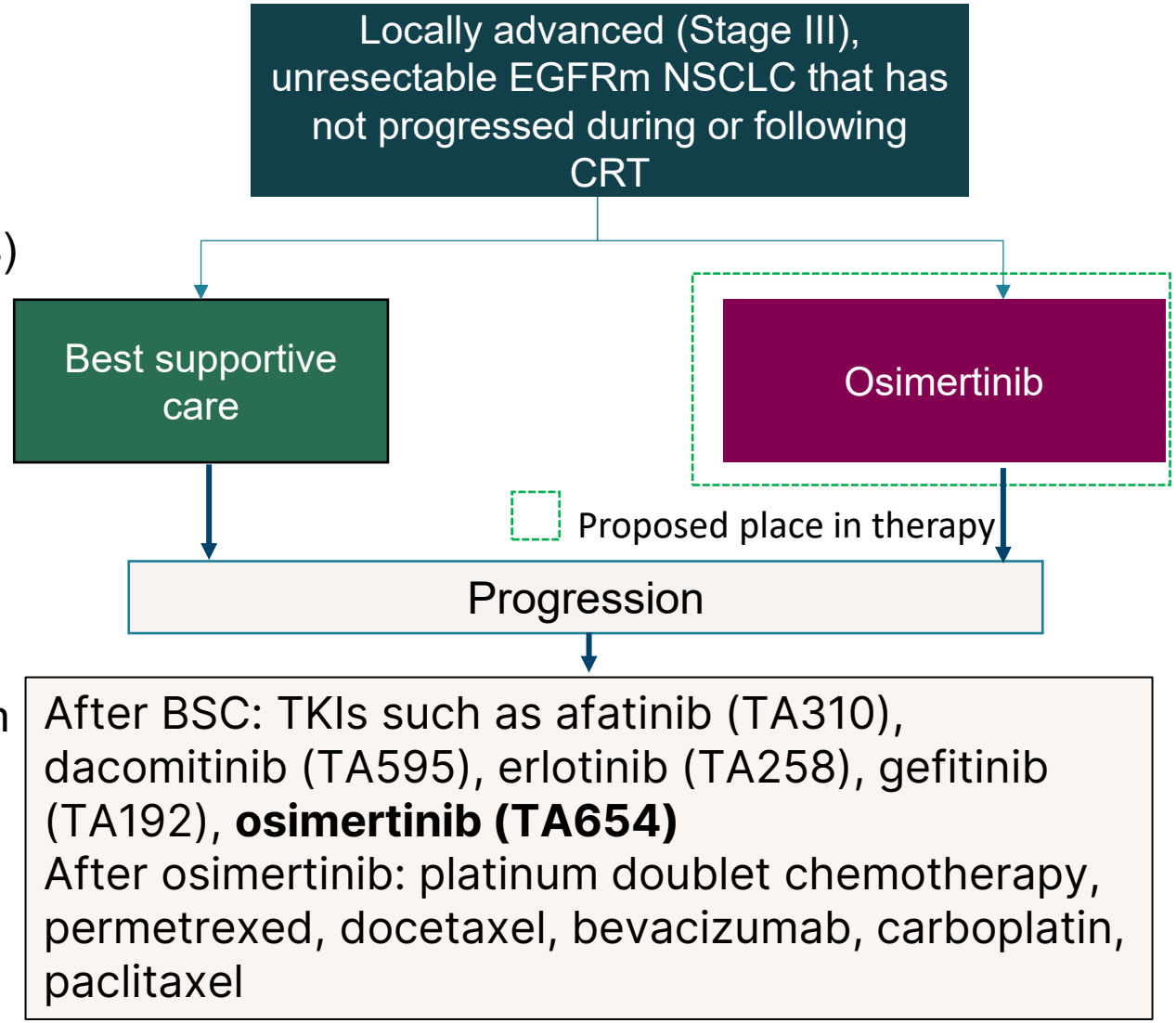
Abbreviations: CRT, chemoradiation; EAG, external assessment group, EGFR, epidermal growth factor receptor

Treatment pathway for EGFRm unresectable NSCLC

Population includes people with Stage III, unresectable, EGFRm NSCLC whose disease has not progressed after platinum-based chemoradiation

- Best supportive care in practice consists of
  - active monitoring (e.g. CT scans every 3 months)
  - may include PET scans or biopsies to confirm recurrence
  - symptom management
- Osimertinib is positioned as a maintenance therapy as an alternative to 'best supportive care'
- After progression, different types of treatment will be given. Unlikely a TKI would be given if osimertinib given as maintenance treatment

Adapted from company submission figure 2



Abbreviations: CRT, chemoradiotherapy; CT, computed tomography; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; NSCLC, non-small cell lung cancer; PET, positron emission tomography; TA, NICE technology appraisal, TKI, tyrosine kinase inhibitor

Osimertenib (Tagrisso, AstraZeneca)

Marketing authorisation (Granted May 2025)	Treatment of adult patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy
Mechanism of action	Osimertenib is a 3rd generation tyrosine kinase inhibitor that selectively targets activating EGFR mutations and the resistance mutation T790M without affecting the wild-type EGFR ↳ Inhibits EGFR phosphorylation and downstream signalling, leading to tumour growth inhibition and cell cycle arrest
Administration	• Osimertinib is available as 40 mg or 80 mg oral tablets. The recommended dose is 80 mg once a day
Price	• List price £5,770 per pack of 30 tablets (identical price for 40mg and 80mg tablets) ↳ A confidential price available via a Commercial Access Agreement

Other Osimertinib NICE recommendations for NSCLC:

- First-line for locally advanced or metastatic EGFR+ NSCLC (TA654) – October 2020
- Second-line for EGFR T790M+ NSCLC (TA653) – October 2020
- Adjuvant treatment after surgery for EGFR+ NSCLC (TA1043) – February 2025

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

ACM1 – Preliminary recommendation and key conclusions

Osimertinib should not be used for the maintenance treatment of locally advanced (stage 3) unresectable non-small cell lung cancer (NSCLC) in adults when the tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, and the cancer has not progressed during or after platinum-based chemoradiotherapy.

Topic	Draft guidance conclusion
Overall Survival	Uncertain – further analyses requested
PPS for BSC group	Modelled using the Weibull distribution
PFS and TTP for osimertinib	Modelled using exponential distribution
PPS for osimertinib	Modelled using Gompertz distribution
TTD for osimertinib	Modelled using the same extrapolation as used for PFS
10-year stopping rule for osimertinib	Removed
Proportion having subsequent treatment	Taken from the LAURA trial
HSUVs	PF: adjusted to align with general UK population norms PD: average of TA654 HSUVs

Abbreviations: BSC, best supportive care; HSUV, health state utility value; KM, Kaplan Meir; PD, progressed disease; PF, progression free; PFS, progression free survival; PPS, post-progression survival; OS, overall survival; TTD, Time to treatment discontinuation; TTP, time to progression

Stakeholder responses to Draft Guidance

Submission from: EGFR+ UK

- Osimertinib following chemoradiation can extend PFS and reduce CNS disease burden
- Predictable and manageable side-effects let people live 'normal' lives.
- Negative recommendation is upsetting for EGFR patients in this situation, and the impact on quality of life is significant.
- Maintenance treatment helps reduce fear associated with recurrence/progression by giving patients a sense of control.

"If I had started Osimertinib after chemoradiation, I would be living with a curative prognosis - without any brain progression. Me and my partner could make plans for our future - a family, work, marathons. A stage 4 diagnosis has changed everything." – EGFR+ UK Patient testimony

Abbreviations: CNS, central nervous system; EGFR, epidermal growth factor receptor; PFS, progression-free survival

Issues resolved as part of DG consultation

Issue	Resolved following ACM1?
Overall survival • Osimertinib rechallenge • Directly incorporating trial data into model	Yes – committee to confirm
Post progression survival for people initially treated with osimertinib	Yes
Proportion receiving subsequent treatments	Yes
Health state utility values (HSUVs)	Yes

ACM2 Key issues for discussion

	Key Issue	ICER impact
1	Post-progression survival for placebo arm	Large
2	Time to progression and progression-free survival for osimertinib	Moderate
3	Osimertinib time to treatment discontinuation (pre-progression)	Moderate
	Committee to confirm resolved:	
4	Overall survival – osimertinib rechallenge	Unknown
5	Overall survival – data source	Unknown

Summary of preferred assumptions for committee, company and EAG

Distribution	Committee ACM1 preferred assumptions	Company updated base case	EAG scenario
Osimertinib PPS	• Gompertz	• Gompertz	• Gompertz
BSC PPS	• Weibull	• Gompertz	• Generalised gamma
BSC post-progression: osimertinib treatment duration	• [redacted] months	• [redacted] months	• [redacted] months
Osimertinib PFS and TTP	• Exponential	• Weibull	• Exponential
Osimertinib pre-progression TTD extrapolation	• Exponential (from model start)	• Exponential (after 36 months of KM data)	• Exponential (from model start)
Osimertinib TTD stopping rule	Removed 10-year stopping rule		
Subsequent treatment rates	Subsequent treatment proportions informed by LAURA trial		
Utilities	PF: adjusted to align with general UK population norms; PD: average of TA654 HSUVs		

Abbreviations: BSC, best supportive care; HSUV, health state utility value; KM, Kaplan Meir; PD, progressed disease; PF, progression free; PFS, progression free survival; PPS, post-progression survival; OS, overall survival; TTD, Time to treatment discontinuation; TTP, time to progression

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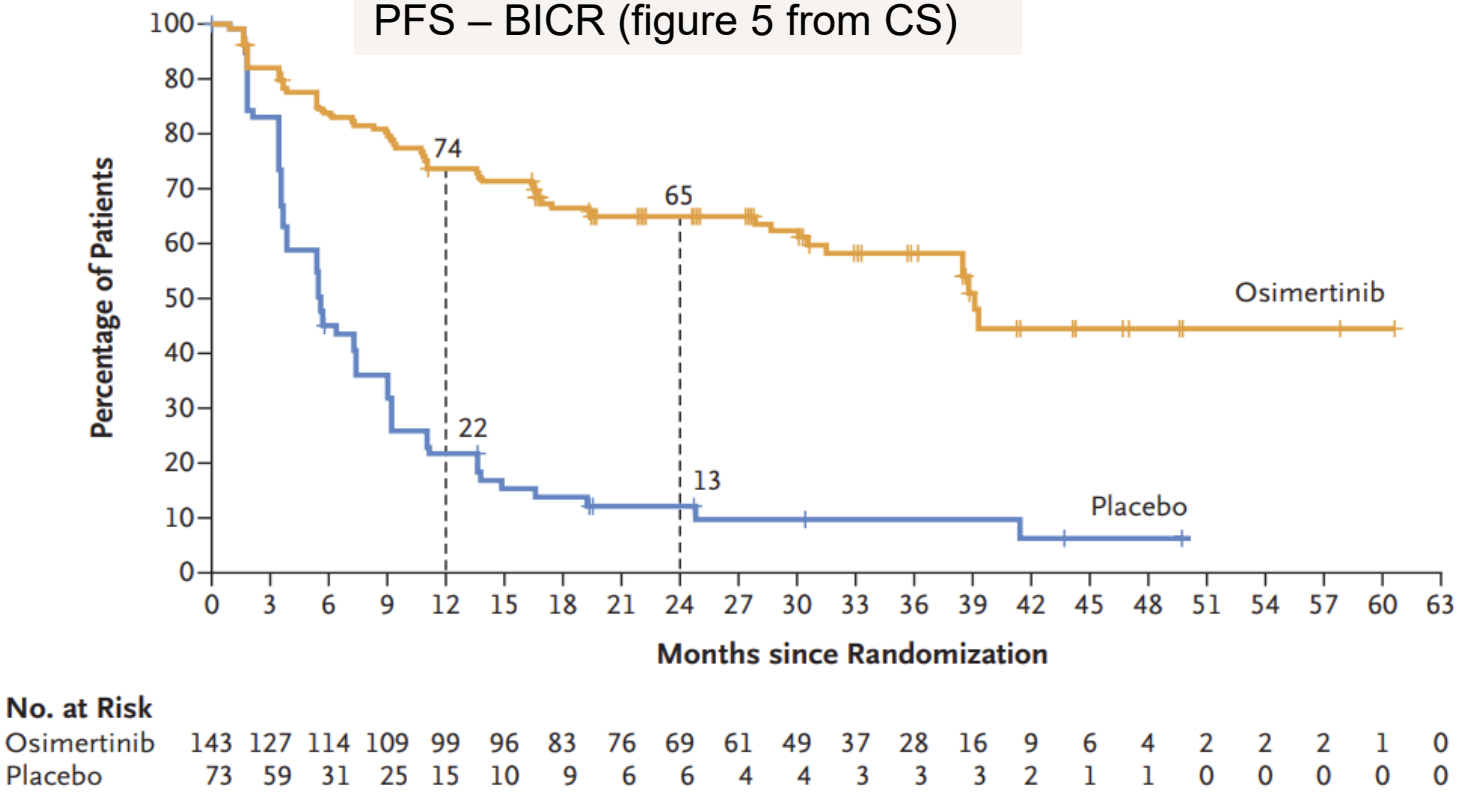
Interim LAURA trial results – PFS (DCO: January 2024)

PFS – BICR (figure 5 from CS)



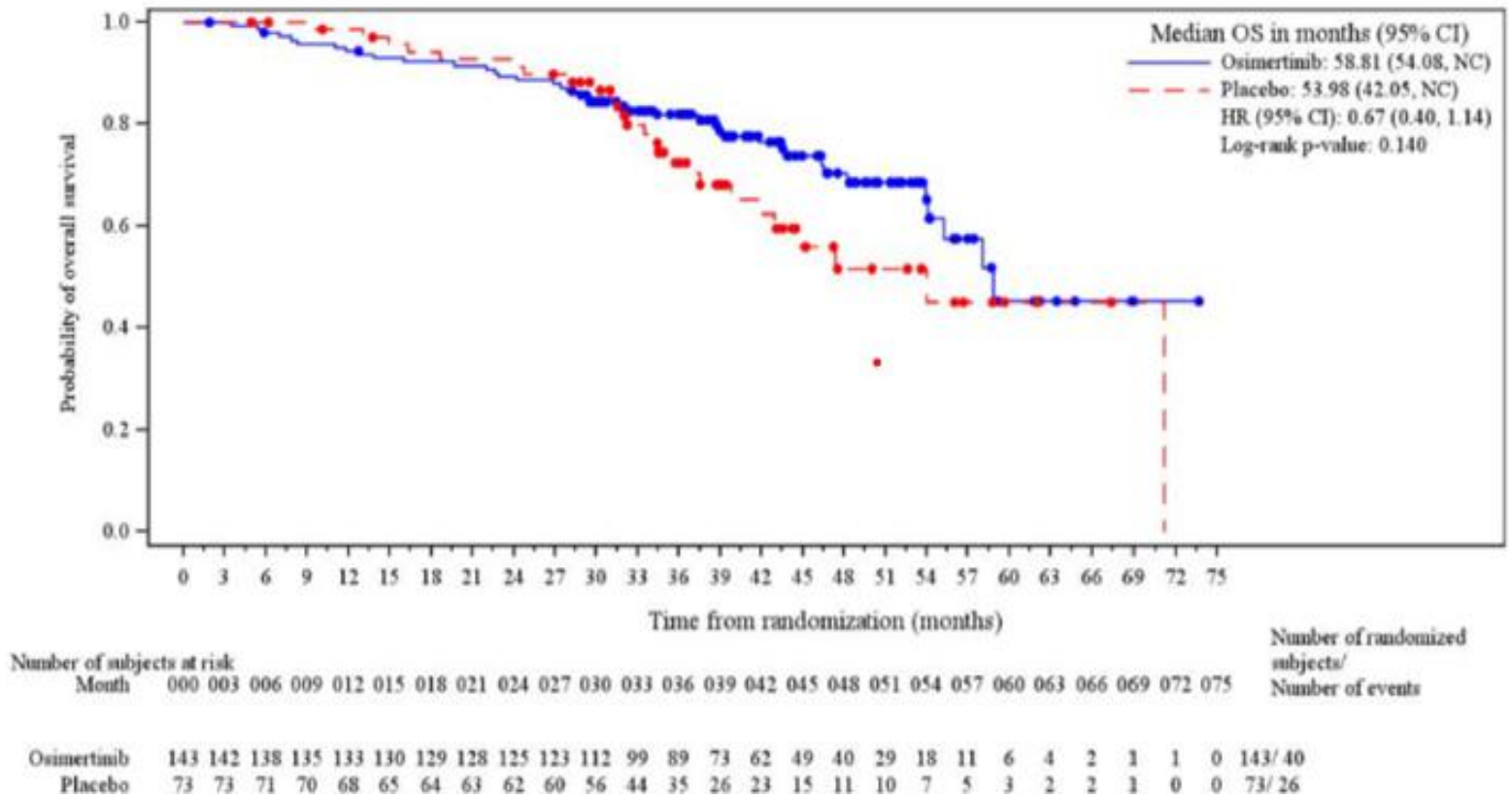
- PFS statistically significant: favours osimertinib (data maturity for BICR PFS: 55.6%)
- KM curve: early sustained separation from 1st RECIST scan at 8 weeks post-randomisation and over follow up
- Investigator assessed analysis: consistent with BICR analysis, statistically significant PFS gain
- Concordance between 2 analyses of PFS was high, with an [redacted]% agreement in the osimertinib arm, and a [redacted]% agreement in the placebo arm

BICR-assessed PFS (primary outcome)	Osimertinib	Placebo
Median (range) follow-up (months)	[redacted]	[redacted]
Number of events (%)	57 (39.9)	63 (86.3)
Median PFS, months (95% CI)	39.1 (31.5 to NE)	5.6 (3.7 to 7.4)
HR (95% CI); p-value	0.16 (0.10 to 0.24); p<0.0001	
PFS rate at 36 months, % (95% CI)	[redacted]	[redacted]

Abbreviations: BICR, blinded independent central review; CI, confidence interval; cs, company submission; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival

Interim LAURA trial results – OS (DCO: November 2024)

OS – figure 1 (CSa)



	Osimertinib	Placebo
No. of events, (%)	40/143 (28%)	26/73 (35.6%)
Median OS (95% CI)	58.8 months (54.1, NC)	54.0 months (42.1, NC)
Hazard ratio (95% CI)	0.67 (0.40, 1.14)	

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CSa, company submission additional evidence; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival

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Company's model overview

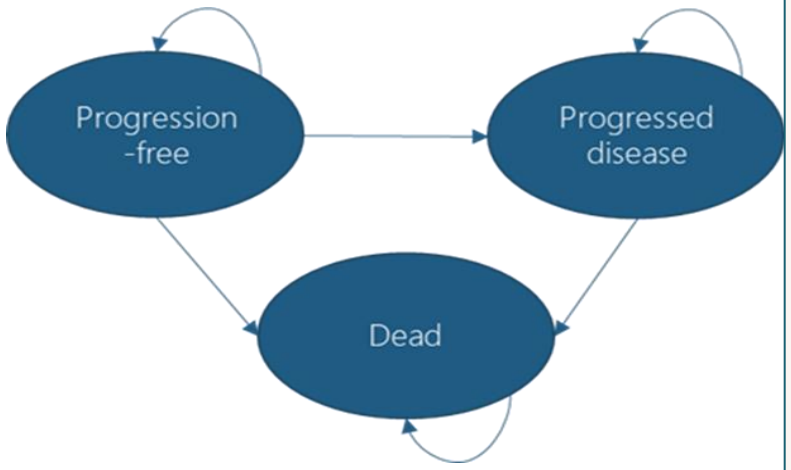

Figure: *Model structure (Figure 17 from CS)*

- All patients enter PF state receiving either osimertinib or placebo
- OS not an input in model; OS is an output of the model OS estimated using 3 endpoints (TTP, PFS and PPS)
- Transition probabilities derived from LAURA trial and vary by treatment arm and over time
- Extrapolated time to TTD data used to incorporate osimertinib treatment costs in PF health state
- Health-state specific values (EQ-5D-5L) inform PF state HR-QoL, adverse event incidence data also used

Transition	LAURA trial data	Notes
PF → PD	Time to progression (TTP)	From BICR-assessed data; fitted parametric curves to TTP data and extrapolated over lifetime horizon
PF → Dead	Difference between progression free survival (PFS) and TTP	Parametric curves fitted to PFS and TTP data and extrapolated over a lifetime horizon. Mortality capped at general population rates
PD → Dead	Post-progression survival (PPS)	Parametric fit to PPS KM data from progressed population

Abbreviations: BSC, best supportive care; CS, company submission; HR-QoL, health-related quality of life; ICER, Incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression free survival; PPS, post-progression survival; QALY, Quality adjusted life year; TTD, treatment discontinuation; TTP, time to progression

See appendix – Technology impact on costs and QALYs

Summary of preferred curve distributions for committee, company and EAG

Distribution	Committee ACM1 preferred assumptions	Company updated base case	EAG scenario
Osimertinib PPS	• Gompertz	• Gompertz	• Gompertz
BSC PPS	• Weibull	• Gompertz	• Generalised gamma
BSC post-progression: osimertinib treatment duration	• [redacted] months	• [redacted] months	• [redacted] months
Osimertinib PFS	• Exponential	• Weibull	• Exponential
Osimertinib TTP	• Exponential	• Weibull	• Exponential
Osimertinib pre-progression TTD	• Exponential (from model start)	• Exponential (after 36 months of KM data)	• Exponential (from model start)

Abbreviations: BSC, best supportive care; Kaplan Meir; PFS, progression free survival; PPS, post-progression survival; TTD, Time to treatment discontinuation; TTP, time to progression

Comparison of LAURA, FLAURA and FLAURA2 trials

	LAURA	FLAURA	FLAURA2
Study Design	Phase III, international, double-blind, randomised	Phase III, international, double-blind, randomised	Phase III, international, open-label, randomised
Population	Adults with histologically confirmed unresectable, stage III NSCLC	Adults with locally advanced or metastatic EGFR mutation-positive NSCLC	Adults with locally advanced or metastatic EGFR mutation-positive NSCLC
Number of participants	216	556	557
Intervention	Osimertinib 80 mg, daily (N=143)	Osimertinib 80 mg, daily (N=279)	Osimertinib 80 mg, daily and platinum-based chemotherapy (N=279)
Comparator	Placebo (N=73)	Standard of care Erlotinib 150 mg, daily Gefitinib 250 mg, daily (N=277)	Osimertinib 80 mg, daily (N=278)
NICE evaluation	ID6223	TA654	TA1060

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

ICER Impact: Large

Key Issue 1: Post-progression survival for placebo arm (1)

Background

- Committee preferred EAG's Weibull over company's Gompertz distribution for PPS for placebo arm

Company

- PPS extrapolated using Gompertz distribution supported by 3 of 5 clinical experts
- EAG suggest Gompertz distribution inappropriate based on comparison between mean PPS in LAURA (stage III disease) to mean OS from FLAURA (1st line metastatic disease)
  - Comparison lacks validity due to differences in treatments received and patient characteristics

 Abbreviations: BSC, best supportive care; DCO, data cut-off; KM, Kaplan-Meier; OS, overall survival; PF, progression-free; PPS, post-progression survival

See appendix – EAG scenario analysis

ICER Impact: Large

Key Issue 1: Post-progression survival for placebo arm (2)

EAG comments

- Company compares LAURA and FLAURA2 to calculate osimertinib treatment duration for people initially treated with BSC
- Value in the model ([redacted] months) is based on [redacted]
  - [redacted] based on clinical advice that LAURA BSC patients in the PPS setting who receive osimertinib will be on treatment longer than those in PF setting of FLAURA or FLAURA2
  - longer survival in LAURA (median LAURA PPS= 41.8 months vs median FLAURA2 OS= 36.7 months
- However, OS data shows sharp decline in LAURA trial placebo KM estimate at the Nov 24 DCO
  - Suggests rapid disease progression and shorter osimertinib treatment than company assumes
  - However updated Nov 24 osimertinib treatment duration unavailable
- EAG explored scenario using shorter osimertinib treatment duration of [redacted] months (LAURA Jan 24 DCO) for people initially treated with BSC (consistent with survival data used in the model)
- Scenario used generalised gamma used to extrapolate BSC PPS → produced appropriate survival estimates

NICE Abbreviations: BSC, best supportive care; DCO, data cut-off; KM, Kaplan-Meier; OS, overall survival; PF, progression-free; PPS, post-progression survival

See appendix – EAG scenario analysis

ICER Impact: Large

Key Issue 1: Post-progression survival for placebo arm (3)

Comparison of mean survival in PD state for patients initially treated with BSC and mean survival for patients treated with osimertinib as first-line treatment in metastatic setting

	Mean survival (undiscounted, months)			
	BSC (post-progression)			Osimertinib (TA654; FLAURA)
	Company base case (Gompertz)	Committee preferred (Weibull)	EAG scenario (Generalised gamma)	Committee preferred assumptions
Osimertinib treatment duration	[redacted]	[redacted]	[redacted]	21.96
Mean survival after discontinuing osimertinib (+ patients who don't receive osimertinib)	[redacted]	[redacted]	[redacted]	34.19 to 38.26
Total survival (months)	[redacted]	[redacted]	[redacted]	56.15 to 60.22

*Adjusted to account for the proportion of patients who did not receive osimertinib after progression

EAG comments on EAG scenario

- Adjusted osimertinib treatment duration for patients in PD health state is similar to TA654
- PPS is slightly worse than TA654; may be pessimistic since patients in LAURA placebo arm generally have less advanced disease upon progression than patients in first-line metastatic setting

Abbreviations: BSC, best supportive care PD, progressed disease; PPS, post-progression survival

ICER Impact: Large

Key Issue 1: Post-progression survival for placebo arm (4)

Comparison of OS for different distributions used to model PPS in the LAURA trial placebo arm

[redacted]

Company comments

- Committee preferred combination results in osimertinib and placebo OS curves crossing at 72 months
- Clinically implausible; agreed UK clinical experts

EAG comments

- no substantial difference in visual fits for LAURA trial OS KM data to model PPS (due to data immaturity), but extrapolations vary considerably

What is the most appropriate osimertinib treatment duration for people initially treated with BSC?
What is the most appropriate distribution for modelling PPS for the placebo arm?

Abbreviations: BSC, best supportive care; DCO, data cut-off; KM, Kaplan-Meier; PPS, post-progression survival; OS, overall survival

ICER Impact: Moderate

Key Issue 2: Time to progression and progression-free survival for osimertinib

Background

- Committee preferred exponential distribution for TTP and PFS; company used Weibull in base case
- Committee requested further analyses of PFS and TTP extrapolations, taking into account PPS extrapolations and resulting OS predictions

Company

- Weibull curve provided a reasonable statistical and visual fit to KM and hazard curves and was considered the most clinically plausible long-term extrapolation of TTP based on clinical expert opinion
- Exponential distribution does not provide a superior fit to the data compared to the Weibull distribution, nor is it supported by clinical opinion
- Figures referenced in DG that highlight high 10-year PFS using Weibull were from a global advisory board
  - UK clinical validation exercise should take precedent for clinical validation of the survival curves
- Provided scenarios using different combinations of curves (see part 2 slides)

EAG comments

- Exponential was only distribution to produce a 10-year PFS estimate (11.6%) within the range estimated by clinicians at company global advisory board (10.0% to 15.0%)
- Exponential distribution is a plausible alternative to Weibull as both have similar statistical fit
- Clinical advice to committee was Weibull PFS estimates at 5-years (38.9%) and 10-years (18.5%) were high, consistent with global advisory board

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Which distribution is best for modelling TTP and PFS for people having osimertinib?

Abbreviations: DG, draft guidance; KM, Kaplan-Meier; TTP, time to progression; PFS, progression-free survival; PPS, post-progression survival; OS, overall survival

ICER Impact: Moderate

Key Issue 3: Osimertinib time to treatment discontinuation (pre-progression)

Background

- At ACM1, committee preferred EAG's approach using the same extrapolation as PFS for TTD
- Committee preferred exponential distribution for PFS, so the same was applied to TTD
  - Company preferred to model PFS using Weibull distribution
- Committee noted company's piecewise approach was plausible but EAG's methodologically preferred

Company

- Maintained piecewise approach- reflects trial evidence and clinical expert consensus
- Modelling directly supported by trial data until 36 months then extrapolation derived from the trial data
- Exponential model curve provides a poor visual fit to the TTD KM data

EAG comments

- TTD should be extrapolated with the same as for PFS
- Company's approach does not reflect the trial evidence as there is no separation between the LAURA trial PFS and TTD KM curves
- Separation occurs at the timepoint the exponential distribution is used to extrapolate TTD in the model rather than at a timepoint informed by clinical evidence
- Modelling separation between PFS and TTD curves in the extrapolation period would require subsequent adjustment to TTP and PFS estimates

Does the committee prefer using the same extrapolation as PFS or a piecewise approach to model TTD?

Abbreviations: KM, Kaplan Meir; PFS, Progression free survival; TTD, Time to treatment discontinuation; TTP, time to progression

ICER Impact: Unknown

Key Issue 4: Overall survival – osimertinib rechallenge

Background

- 44.4% in osimertinib-arm who stopped treatment had subsequent EGFR-TKI (DCO Jan 2024) and 23.8% had retreatment with osimertinib
- Clinical experts advised that this treatment sequence would not occur in NHS practice
- Committee requested a rechallenge adjustment to accurately estimate the survival benefit of osimertinib

Company

- RPSFT method used for crossover adjustment analysis as IPCW and TSE methods could not be applied
- [redacted]
- [redacted]
- [redacted]

EAG comments

- [redacted]
- Company analysis assumes effect of osimertinib is the same for patient's first exposure (after switching from placebo) or rechallenge (after progression on osimertinib)
- This offers conservative assumption when adjusting for effect of subsequent osimertinib

What is the committee's view on the impact of post-progression osimertinib treatment on OS?

Abbreviations: EGFR, estimated glomerular filtration rate; OS, overall survival; PFS, Progression-free survival; RPSFT, rank-preserving structural failure time; TKI, Tyrosine kinase inhibitor; TSE, two-stage estimation

See appendix – Crossover adjustment curves and Crossover adjustment methodology

ICER Impact: Unknown

Key Issue 5: Overall survival – including trial data

Background

- Committee noted that OS data not directly modelled and that real-world data and data from LAURA may reduce uncertainty in modelling assumptions
- Requested scenario where OS directly modelled (including crossover adjustment)

Company

- Changing the model structure to directly incorporate immature OS data would not reduce uncertainty
- Semi-Markov structure allows OS endpoint to be extrapolated as a function of TTP and PPS, introducing a structural link between mortality and earlier non-fatal events
- Committee concluded that model was "reasonable and consistent with models used in other oncology NICE technology appraisals guidance at this line of treatment"

EAG comments

- Using currently available data in a PSM is unlikely to materially reduce uncertainty
- Survival extrapolation uncertainty likely to persist (Nov 2024 OS data maturity was 31%)
- Updated subsequent treatment data from the Nov 2024 DCO would be informative; but company were unable to provide this

Does the committee agree that modelling OS using currently available OS data would not materially reduce uncertainty?

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Abbreviations: DCO, data cut-off; OS, overall survival; PFS, Progression-free survival; PPS, post-progression survival; PSM, partitioned survival model; TTP, time to progression

Summary of preferred assumptions for committee, company and EAG

Distribution	Committee	Company	EAG scenario
Osimertinib PPS	• Gompertz	• Gompertz	• Gompertz
BSC PPS	• Weibull	• Gompertz	• Generalised gamma
BSC post-progression: osimertinib treatment duration	• [redacted] months	• [redacted] months	• [redacted] months
Osimertinib PFS and TTP	• Exponential	• Weibull	• Exponential
Osimertinib pre-progression TTD extrapolation	• Exponential (from model start)	• Exponential (after 36 months of KM data)	• Exponential (from model start)
Osimertinib TTD stopping rule	Removed 10-year stopping rule		
Subsequent treatment rates	Subsequent treatment proportions informed by LAURA trial		
Utilities	PF: adjusted to align with general UK population; PD: average of TA654 HSUVs		

EAG comments

- Updated company base case uses the committee preferred assumptions for subsequent treatment proportions, patients initially treated with BSC receiving osimertinib post-progression (now [redacted] from [redacted])
  - However, PPS for patients treated with BSC remains unchanged → not considered plausible

Abbreviations: BSC, best supportive care; HSUV, health state utility value; KM, Kaplan Meir; PD, progressed disease; PF, progression free; PFS, progression free survival; PPS, post-progression survival; OS, overall survival; TTD, Time to treatment discontinuation; TTP, time to progression

Committee decision making

What are the committee's preferred assumptions

Overall survival	• What is the committee's view on the impact of post-progression osimertinib treatment on OS? • Does the committee agree that modelling OS using currently available OS data would not materially reduce uncertainty?
Post-progression survival for BSC arm	• What is the most appropriate osimertinib treatment duration for people initially treated with BSC? • What is the most appropriate distribution for modelling PPS for the placebo arm?
Osimertinib pre-progression Time to treatment discontinuation	• Does the committee prefer using the same extrapolation as PFS or a piecewise approach to model TTD?
TTP and PFS extrapolation	• Which distribution is best for modelling TTP and PFS for people having osimertinib?
ICER threshold	• What is committee's preferred ICER threshold?
Equality	• Are there any equalities issues which can be addressed in this appraisal?

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Abbreviations: BSC, best supportive care; CNS; central nervous system; DSU, decision support unit; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, Progression free survival; PPS, post-progression survival; TTD, Time to treatment discontinuation; TTP, time to progression

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Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

Patient Access Scheme discounts

- There are confidential discounts in place for osimertenib and for other medicines used in the model
- The company's updated base case ICER is within the range NICE normally considers cost-effective
- The EAG's base case ICER is above the range NICE normally considers acceptable

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation

Supplementary appendix

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Technology impact on costs and QALYs

Technology affects <u>costs</u> by:

- Increased treatment costs
- Increased resource-use costs

Technology affects <u>QALYs</u> by:

- Increased progression-free survival (PFS)
- Increased overall survival (OS)

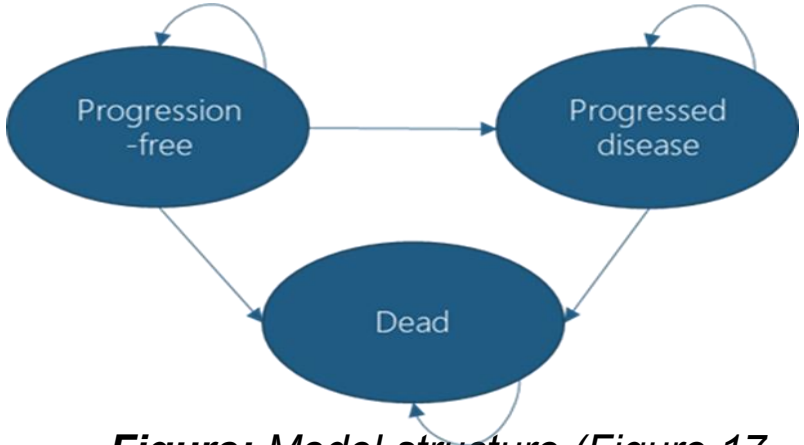

Figure: *Model structure (Figure 17 from CS)*

Assumptions with <u>greatest ICER effect</u>:

- Long-term treatment duration assumptions and time on osimertinib
- Choice of distribution to model time to progression (TTP) and PFS in osimertinib arm

Back to – Company's model overview

Abbreviations: CS, company submission; ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life year

EAG scenario analysis

Back to – Key issue 1: PPS for placebo arm

EAG comments

- Patients in the LAURA trial placebo arm may be treated with osimertinib for a similar length of time to patients in the first-line metastatic setting and have similar survival
- Sharp decline in LAURA trial placebo KM estimate at the Nov 24 DCO; 73% at 3 years to 52% at 4 years
  - Suggests shorter osimertinib treatment duration than company assumes and overestimation of survival using Gompertz to model PPS
- Company unable to provide further data from Nov 24 DCO to explain change in LAURA trial OS KM data

EAG scenario included the following changes to committee preferred assumptions from ACM1

Osimertinib treatment duration

- Osimertinib treatment duration [redacted] months for people initially treated with BSC (LAURA Jan 24 DCO) rather than [redacted] months based on [redacted] (committee preferred at ACM1)
  - Chosen to be consistent with data used in the company model to estimate PPS

Distribution selection

- Used Generalised gamma instead of Weibull for BSC PPS estimates
  - Produces PPS estimates broadly in line with survival estimates from NICE appraisal TA654
  - Statistical fit is similar to the Weibull and Gompertz distributions
  - 10-year OS estimate ([redacted]) approximates the midpoint of the estimates suggested by clinicians ([redacted]) consulted by the company in response to draft guidance

Abbreviations: BSC, best supportive care; DCO, data cut-off; KM, Kaplan-Meier; OS, overall survival; PFS, Progression-free survival; PPS, post-progression survival

ICER Impact: Unknown

Key Issue 4: Crossover adjustment curves

LAURA FAS OS with and without adjustment for subsequent osimertinib in the osimertinib arm

Back to – Overall survival: crossover adjustment

Abbreviations: FAS, full analysis set; OS, overall survival; RPSFT, rank-preserving structural failure time; QD, every day

Crossover adjustment methodology

Back to – Overall survival: crossover adjustment

Company

- In LAURA trial patients were randomised 2:1 to osimertinib or placebo and a number of patients received subsequent treatment with osimertinib in both treatment groups
- RPSFT method was used to estimate effect of subsequent treatment with osimertinib
- Acceleration factor for the impact of receiving subsequent osimertinib was estimated then applied to post-switch times for subsequent osimertinib receipt in the intervention arm
- Acceleration factor is the degree to which being on subsequent osimertinib changes survival
- Exponential of psi is the amount post-switch times are multiplied by to 'accelerate' them to account for survival having been extended by receiving subsequent therapy
- To estimate the proportion of time on osimertinib for each patient:
  - For patients randomised to placebo who did not receive subsequent therapy with osimertinib, the proportion of time on osimertinib is set to 0
  - For patients randomised to placebo who received subsequent therapy with osimertinib, the proportion of time on osimertinib is calculated as (OS time - time prior to subsequent therapy) / OS time;
  - For patients randomised to osimertinib, the proportion of time on osimertinib is set to 1

Use of osimertinib as a subsequent therapy (DCO: 29 Nov 24)

Randomised treatment arm	n (% total subjects randomised)*
Osimertinib	[redacted]
Placebo	[redacted]

*Includes patients receiving osimertinib [redacted] cond subsequent treatment

Acceleration factor

Method	psi (95% CI)	exp(psi) (95% CI)
Osimertinib	[redacted]	[redacted]
Placebo	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; DCO, data cut-off; OS, overall survival; RPSFT, rank-preserving structural failure time

Osimertinib 10-year stopping rule

Background

- Committee concluded in ACM1 that a fixed 10-year stopping rule was not appropriate for osimertinib treatment

Company

- Updated base case and scenarios provided have 10-year stopping rule removed in response to committee and EAG feedback
- 10-year stopping rule based on clinical expert feedback that indefinite osimertinib treatment is unlikely
- Without this assumption, exponential model in company base case predicts 11% of patients still receiving treatment at 10 years and 20% for EAG's base case model → considered clinically implausible
- Osimertinib not without toxicity, clinicians expected patients may be taken off treatment after 3-5 years even if progression-free

EAG comments

- Company's argument that some patients may discontinue after 3-5 years of PFS is speculative
- No evidence presented to support treatment discontinuation due to toxicity

Abbreviations: PFS, Progression free survival

Managed access

Criteria for 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

Feasibility of managed access

Company submission identifies potential uncertainties and evidence that could be addressed in managed access. Funding through Cancer Drugs Fund available.

Feasibility of managed access: key uncertainties

Key Issue	Uncertainty	Impact on ICER	Feasible Data Source	Notes
OS (3)	OS data immature (31% maturity) and not directly incorporated in economic model. Uncertain long-term impact	Unknown	LAURA trial	Managed access allows OS data (≥60%) to be collected and incorporated into the model
PPS for placebo (4) & osimertinib (6)	PPS for BSC has greatest ICER impact. Estimates uncertain due to immature data (21%) and high crossover (81%)	High	LAURA trial	Limited to ≤5 years data → extrapolation still required, but uncertainty would reduce
TTD (7)	TTD extrapolated beyond 36 months using exponential. PFS and TTD curves diverge. A 10-year stopping rule was applied, not part of trial protocol	Moderate	LAURA trial / committee judgement	SACT can capture real-world TTD, but not PFS. Further trial data may strengthen curve fitting. Committee judgements still needed
Subsequent treatments (8)	Estimates based on expert opinion, lower than trial data. NHS use may vary	Moderate	SACT dataset	SACT could clarify real-world subsequent treatment rates and sequencing → improved modelled costs and PPS assumptions

Abbreviations: OS, overall survival, PFS, progression-free survival; PPS, post=progression survival; TTD, time to treatment discontinuation