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

PART 1
Redacted for screen

HST committee [19th June 2025]

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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

NICE National Institute for Health and Care Excellence

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

Patient perspectives

Submissions from Roy Castle Lung Cancer Foundation, EGFR+ UK, & patient expert

Effects on patients and carers

- Psychological impact of coming to terms with poor outcomes and limited options
- EGFR+ NSCLC often affects younger people (including women with young children), increasing emotional and financial impact
- Stigma associated with lung cancer remains a concern; patients report feeling judged despite being non-smokers or otherwise healthy

Current care

- After chemoradiation, many patients placed on active monitoring
    - This can feel like "waiting for the other shoe to drop," creating distress and uncertainty about recurrence

Osimertinib

- Convenient oral treatment. Generally manageable side effects (e.g. rash, diarrhoea, fatigue)
    - But some side effects (especially diarrhoea) can be long-term and debilitating for some – "dreaded unpredictable, vicious diarrhoea was the worst…it completely drained me"
- Seen as a reassuring option that helps reduce recurrence risk, particularly CNS metastases, and supports a return to normal routine

"Not doing anything feels like such a risk. I can't stop worrying about if or when it will come back"

"Being on osimertinib and having regular scans gives me invaluable reassurance… I feel like I'm doing something to keep my cancer at bay"

Osimertinib "gave me a second chance to live… I got to spend time with my loved ones."

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

Clinical perspectives

Submissions from British Thoracic Oncology Group, Association of Respiratory Nurses & clinical expert

Current treatment and unmet need

- After CRT (often with curative intent) standard care is active monitoring and no treatment
- People with EGFR mutation-positive NSCLC have worse outcomes after CRT than those with other tumour types
- Unmet need: Relapse is common and no current targeted maintenance options
    - Durvulamab used off-label but ineffective. Toxicity risk if osimertinib used subsequently

"This should be regarded as a step change... The vast majority of patients relapse quickly on surveillance. osimertinib can delay that significantly"

Use of Osimertinib

- Osimertinib already widely used in NHS in metastatic and adjuvant settings
    - Introducing it post-CRT is a logical step requiring no major infrastructure change
- Expected to delay progression both local and distant relapse, improve CNS control and preserve quality of life
- Osimertinib offers a "step change" in management by extending treatment options. Will likely replace surveillance or off-label durvalumab use in eligible patients
- EGFR testing already standard; use post-CRT aligns with evolving NHS lung cancer pathways

"It's already used post-surgery and in metastatic settings. This use after chemoradiation is a natural progression in EGFR-positive disease"

Abbreviations: CNS, central nervous system; CRT, chemoradiation; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; NSCLC, non-small cell lung cancer

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

Are there any equalities issues which can be addressed in this technology appraisal?

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

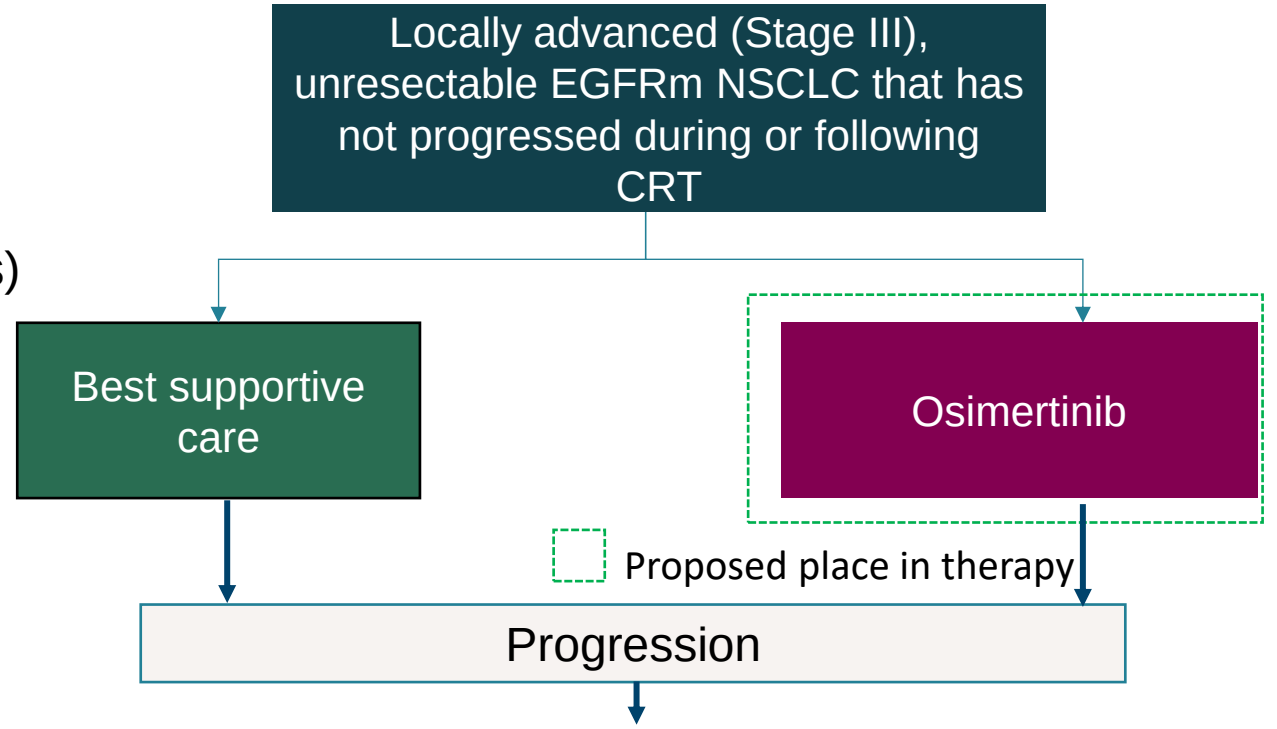
Treatment pathway for EGFRm unresectable NSCLC

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

- Best supportive care 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. Not likely a TKI would be given if osimertinib given as maintenance treatment

- Does this pathway represent NHS practice?
- Would a TKI be given after progression for people who have osimertinib as a maintenance treatment?

Adapted from company submission figure 2



1st Line: TKIs after BSC only, such as afatinib (TA310), dacomitinib (TA595), erlotinib (TA258), gefitinib (TA192), osimertinib (TA654)
Other options: platinum doublet chemotherapy, permetrexed, docetaxel, bevacizumab, carboplatin, paclitaxel

Abbreviations: 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

Osimertinib is currently recommended by NICE for the treatment of NSCLC in the following indications:

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

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

Decision problem

	Final Scope	Company	EAG comments
Population	Adults with EGFR mutation-positive (exon 19 deletion or exon 21 [L858R] substitution) locally advanced unresectable NSCLC whose disease has not progressed after platinum-based CRT	As per final scope	Agree
Intervention	Osimertinib	As per final scope	Agree
Comparators	• Durvalumab (for people who had concurrent chemoradiation therapy and have PD-L1 positive NSCLC) • Best supportive care	Best supportive care only Rationale: durvalumab not relevant in UK practice for EGFRm NSCLC after CRT	Agree durvalumab not routinely used in practice; exclusion appropriate given expert and guideline input
Outcomes	OS, PFS, DFS, response rates, AEs, HRQoL	Excludes DFS: DFS not assessed in LAURA and not used in this setting	Agree DFS not appropriate or relevant in this population
Subgroups	If evidence allows: CCRT vs SCRT; PD-L1 status; disease stage; new vs recurrent; prior treatments; EGFR mutation type	LAURA trial included: age, sex, smoking status, race, CRT type, disease stage, EGFR mutation, CRT response	PFS subgroup data presented for 3 NICE-specified subgroups

Abbreviations: AE, adverse event; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; HRQoL, health-related quality of life; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SCRT, sequential chemoradiotherapy

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Key issues

Issue		ICER impact
1	Generalisability of trial to the NHS	Unknown
2	Representativeness of LAURA trial placebo arm	Unknown
3	Overall survival	Unknown
4	Post-progression survival for placebo arm	Large
5	Time to progression and progression-free survival	Moderate
6	Post progression survival for people initially treated with osimertinib	Small
7	Osimertinib time to treatment discontinuation	Moderate
8	Subsequent treatments	Moderate
9	Health state utility values (HSUVs)	Small
10	Managed access	N/A

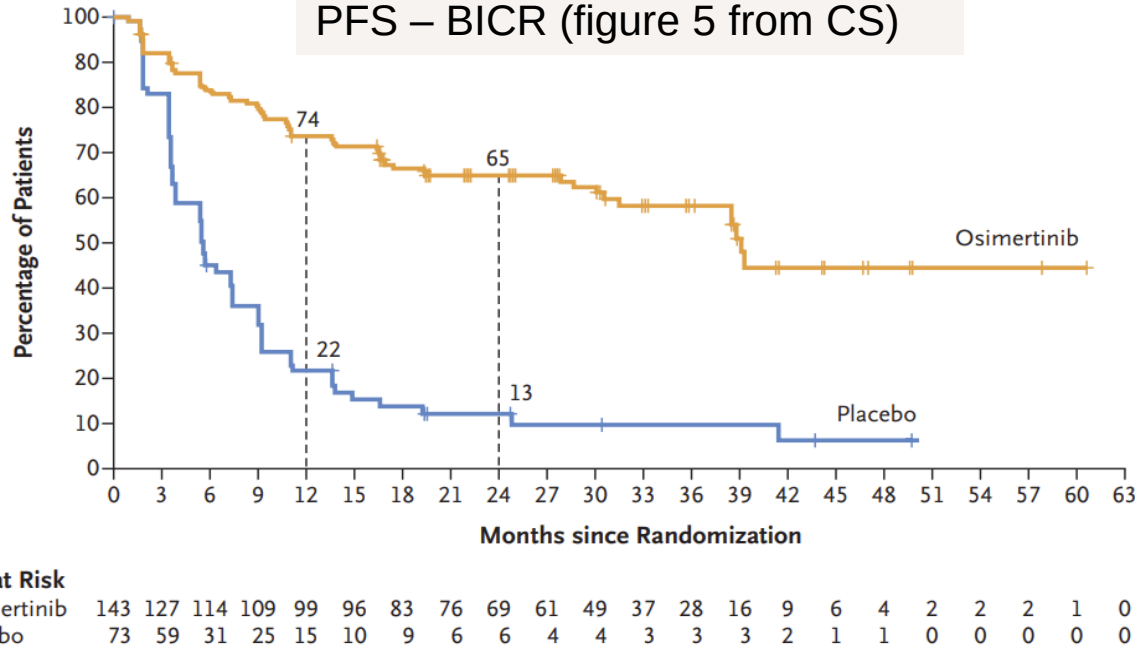
Key clinical trial – LAURA (n=216)

Design	Phase III, international, double-blind, randomised
Population	Adults (≥18 years [and ≥20 years in Japan]) with histologically confirmed unresectable, stage III NSCLC. Disease positive for one of two common EGFR-sensitising mutations (Ex19del or L858R) either alone or in combination with other EGFR mutations • No progression after chemoradiation • World Health Organisation performance status 0 to 1
Intervention	Osimertinib 80mg daily (n=143) •Dose reductions to 40mg daily if clinically significant adverse events or unacceptable toxicity •Can continue osimertinib treatment post-BICR-confirmed progression
Comparator	Placebo (n=73): Permitted to switch to osimertinib after BICR-confirmed progression
Locations	121 centres across 17 countries in Europe, Asia-Pacific, North America and South America
Outcomes	Progression-free survival (primary endpoint), OS, CNS PFS, ORR, DoR, depth of response, DCR, TTDM, TTD, PFS2, TFST, TSST, time to symptom deterioration, symptom improvement rate, CFB for PRO symptom scores, EQ-5D-5L
Role in analysis	Primary source of clinical effectiveness evidence and the only source of time-to-event data for PFS, TTD, and OS used in the company's base case economic model. EAG based survival extrapolations and scenario analyses on LAURA trial data

Abbreviations: BICR, blinded independent central review; CFB, change from baseline; CNS, central nervous system; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; Ex19del, exon 19 deletion; L858R, substitution of a leucine with an arginine at position 858 in exon 21; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy; TTDM, time to death or distant metastases; TTD, time to treatment discontinuation or death

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

PFS – BICR (figure 5 from CS)



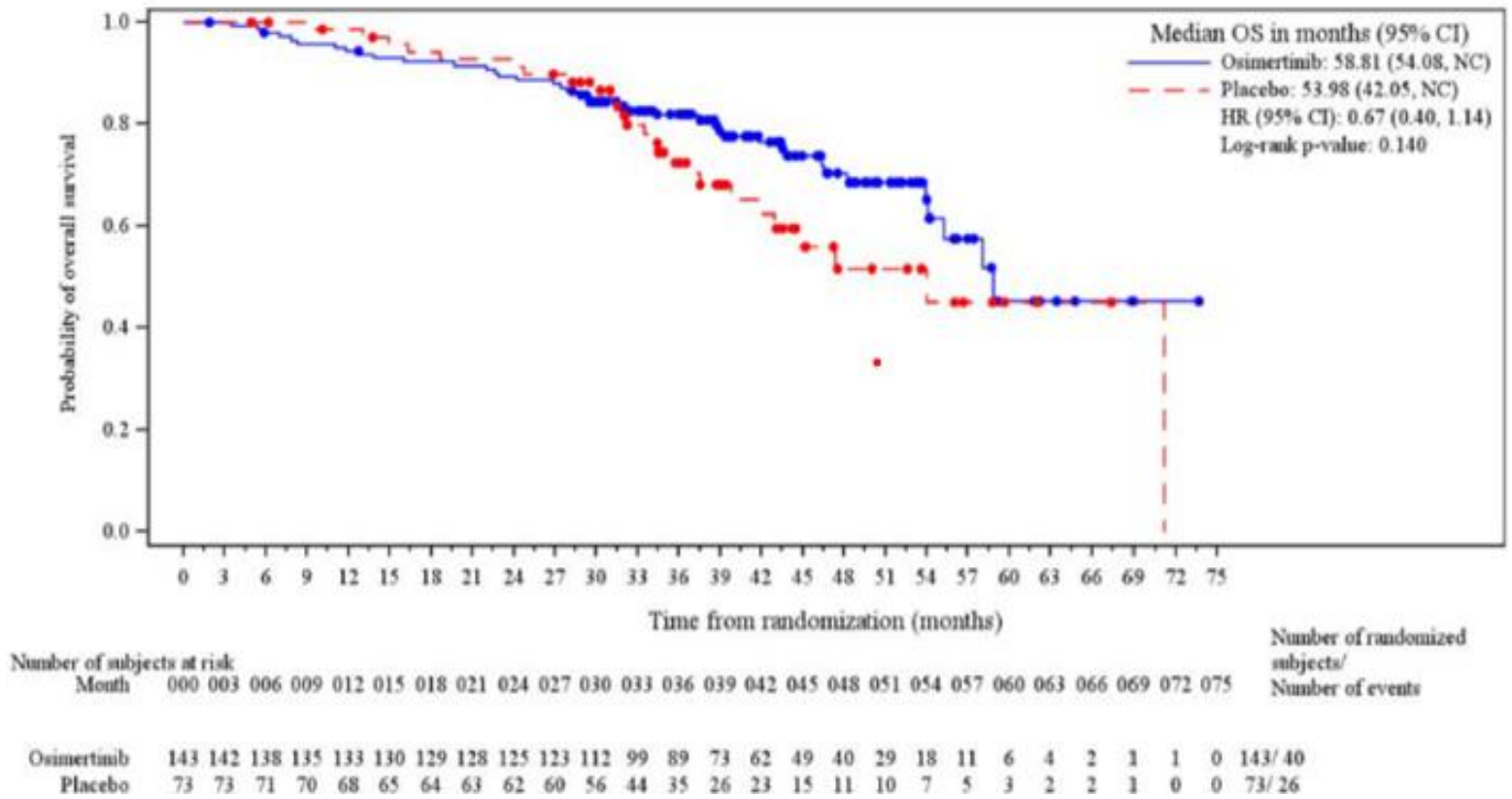
- PFS statistically significant: favours osimertinib (data maturity for BICR PFS: 55.6%)
- KM curve: early sustained separation from 1st RECIST scan at 8 weeks post-randomisation and over follow up
- Investigator assessed analysis: consistent with BICR analysis, statistically significant PFS gain
- Concordance 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]
Investigator-assessed PFS		
Number of events, n (%)	62 (43.4)	63 (86.3)
Median PFS (months) (95% CI)	38.9 (26.7 to NE)	7.3 (5.5 to 10.3)
HR (95% CI); p-value	0.19 (0.12 to 0.29); p<0.001	

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

EAG critique of LAURA trial results

Placebo arm may underestimate NHS outcomes

- Statistically significant PFS benefit for osimertinib vs placebo (but expected as treatment vs. placebo)
- EAG agreed placebo a valid proxy for BSC, but noted placebo arm had “poor” PFS compared to NHS active monitoring
- Median PFS in placebo arm (BICR-assessed: 5.6 months) lower than reported in 5 UK-relevant real-world studies (range: 9.6 to 16.9 months)
- Some comparator studies defined PFS from CRT start, others (PACIFIC, SOLUTION) aligned with LAURA’s approach of defining PFS from CRT end

OS benefit uncertain

- OS showed numerically longer survival with osimertinib, but difference not statistically significant
- 80.6% of placebo arm crossed over to open-label osimertinib, which may confound OS interpretation
- Clinical advice: crossover reflects NHS practice, but 29% of osimertinib arm also received subsequent treatment including rechallenge → this may not reflect NHS care

EAG conclusions

- LAURA PFS results strongly favour osimertinib, but OS benefit unclear due to data immaturity (19.9% mature at Jan 2024, and 31% at Nov 2024) and post-progression treatments
- Generalisability of placebo arm outcomes to NHS practice uncertain due to comparatively short PFS

Abbreviations: PSA, Probabilistic sensitivity analysis; QALY, Quality adjusted life year;

Key Issue 1: Generalisability of trial to the NHS

ICER Impact: Unknown

Background

- LAURA trial had a high proportion of Asian patients and no Black patients

Company

- Considered LAURA trial population representative of NHS clinical practice
- No adjustments made to reflect ethnic diversity differences between LAURA and NHS populations

Baseline characteristics	Osimertinib (n=143) (%)	Placebo (n=73) (%)
Female, n	90 (62.9)	42 (57.5)
Age (years), median (range)	62.0 (36 to 84)	64.0 (37 to 83)
Asian	116 (81.1)	62 (84.9)
White	20 (14.0)	10 (13.7)
Black	0 (0)	0 (0)
Other	7 (4.9)	1 (1.4)
WHO PS 0	80 (55.9)	31 (42.5)
WHO PS 1	63 (44.1)	42 (57.5)
AJCC stage: Stage IIIA	52 (36.4)	24 (32.9)
AJCC stage: Stage IIIB	67 (46.9)	38 (52.1)
AJCC stage: Stage IIIC	24 (16.8)	11 (15.1)

EAG comments

- Clinical advice indicated that this may not affect treatment effectiveness; but small number of non-Asian patients (n=27 osimertinib; n=11 placebo) makes interpretation uncertain
  - Non-Asian subgroup, PFS HR = 0.48 (95% CI: 0.20 to 1.19)
  - Asian subgroup, PFS HR = 0.20 (95% CI: 0.13 to 0.29)
- Further clinical opinion needed to confirm applicability to NHS population

Is the LAURA trial generalisable to the NHS?

Abbreviations: AJCC, American Joint Committee on Cancer; CS=company submission; WHO PS=World Health Organization performance status HR, hazard rate; PFS, Progression-free survival

ICER Impact: Unknown

Key Issue 2: Representativeness of LAURA trial placebo arm

Background

- LAURA placebo arm outcomes used as comparator for modelling cost effectiveness
- Validating that these outcomes reflect NHS best supportive care (BSC) is important to avoid bias

Company

- Used LAURA placebo arm PFS as main comparator in economic model
- Supplemented with a literature review to support comparability

EAG comments

- Clinical advice to company described placebo arm PFS as “poor” compared with NHS expectations
- 6 studies identified by company showed better PFS outcomes than LAURA placebo arm
  - In 1 study, (Neal et al) people received an EGFR-TKIs following CRT → unsuitable proxy for placebo arm in LAURA
- If LAURA placebo PFS underestimates NHS outcomes, ICER may be underestimated
- Further clinical input needed to confirm whether LAURA placebo results reflect NHS BSC practice

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PFS, Progression-free survival

Reported median PFS in placebo arms of trials

Study name	Population (n), design	Intervention	Median PFS (months)	PFS rates (95% CI)	PFS measured from
LAURA (BICR)	EGFRm+ Stage III unresectable NSCLC, no progression post-CRT (n=73). Prospective	Placebo	5.55 (3.71–7.4)	2 year: 12.5% (5.9 to 21.6). 3 year: [redacted]	Completion of CRT
LAURA (Investigator)	Same as above	Placebo	7.3 (5.5–10.3)	2 year: & 3 year: [redacted]	Completion of CRT
PACIFIC (EGFRm subset)	EGFRm+ Stage III unresectable NSCLC, no progression post-CRT (n=11). Prospective	Placebo	10.9 (1.9–NE)	NR	Completion of CRT
SOLUTION	EGFRm+ Stage III unresectable NSCLC, no progression post-CRT, pre-immunotherapy era (n=29). Retrospective	BSC	16.9 (NR)	3–4 year: ~20%	Completion of CRT
Tanaka (2015)	EGFRm+ Stage III adenocarcinoma, no progression post-CRT (n=29). Retrospective	Active monitoring	9.8 (7.6–19.0)*	2-year: 7.7%	Start of CRT
Nassar (2024)	EGFRm+ Stage III unresectable NSCLC, no progression post-CRT (n=47). Retrospective	Active monitoring	9.7 (6.1–12.0)*	2-year: 27%	Start of CRT
Akamatsu (2014)	EGFRm+ Stage III unresectable NSCLC, no progression post-CRT (n=13). Retrospective	Active monitoring	9.6 (NR)*	NR	Start of CRT

- LAURA trial calculated PFS from end of CRT → difference in timing = PFS estimates in comparator studies include both treatment time and post-treatment monitoring, LAURA only measures disease progression after CRT is complete
- Studies that measured from the start of CRT may appear longer as more time is counted before progression

Does the placebo arm in LAURA underestimate PFS?

Abbreviations: BICR, blinded independent central review; BSC, best supportive care; CI, confidence interval; CRT, chemoradiation; CS, company submission; EGFRm, epidermal growth factor receptor mutation; NE, not estimable; NR, not reported; NSCLC, non-small cell lung cancer; PFS, progression-free survival

ICER Impact: Unknown

Key Issue 3: Overall survival

Background

- Initial OS data (DCO 5 Jan 2024, 19.9% maturity, 43 deaths [n=216]) showed non-significant benefit (HR=0.81; CI: 0.42–1.56), confounded by 80.6% crossover from placebo to osimertenib
- Updated OS data (DCO 29 Nov 2024, 31% maturity) submitted post-EAR to support model assumptions (78% crossover from placebo to osimertinib). Median OS: osimertinib 58.8 months (CI: 54.1, NC) vs placebo 54.0 months (CI: 42.1, NC); HR=0.67 (CI: 0.40–1.14)

Company

- KM curves show improved OS benefit with osimertinib; company considers these consistent with modelled assumptions. Acknowledged crossover and noted OS not directly used in model

EAG comments

- Nov 2024 data suggest improved OS, but absence of updated post-progression data limits interpretation
- Mean osimertinib duration for placebo post-progression (Jan 2024: [redacted] months) lower than assumed (~[redacted] months), affecting cost-effectiveness
- Rechallenge: 44.4% osimertinib-arm received subsequent EGFR-TKI (Jan 2024), 23.8% of these received osimertinib again after discontinuation. Nov 2024 data shows people receiving osimertenib = 29.7%
- Osimertinib rechallenge not permitted in NHS, unlikely alternative EGFR-TKI would be used
- Costs of subsequent EGFR-TKI have not been included in model for patients treated with osimertinib
- Unclear if improved survival reflects a true benefit or effects of treatment after progression

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Abbreviations: CI, confidence interval; DCO, data cut-off; EAG, External Assessment Group; EAR, EAG report; HR, hazard ratio; ICER, incremental cost effectiveness ratio; NC, not calculable; OS, overall survival; PFS, Progression-free survival

ICER Impact: Unknown

Key Issue 3: Overall survival

[redacted]

Company comments

- Modelled OS (output based on 3 endpoints) closely aligns with updated KM data for osimertinib & overestimates survival for placebo.
- Results support plausibility of survival model

EAG comments

- OS estimates considered unstable due to low data maturity and uncertainty around subsequent treatments
- Observed changes in OS not fully explained without access to updated subsequent treatment data

What is the committee's view on the modelled survival benefit with osimertinib?

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Company's model overview (1)

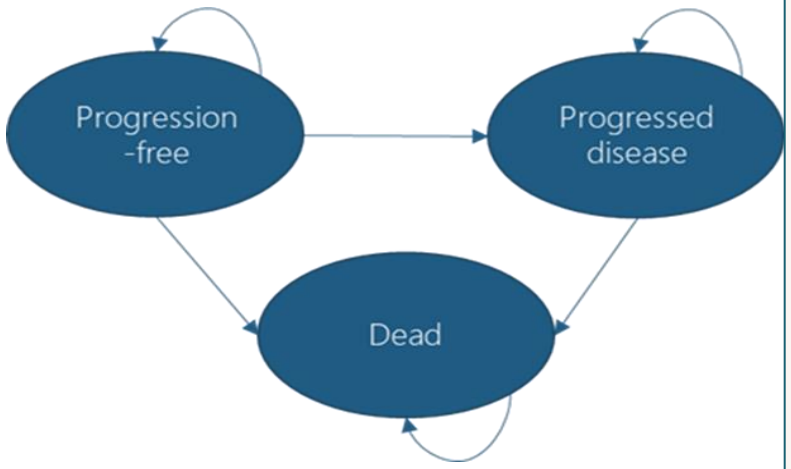

Figure: *Model structure (Figure 17 from CS)*

- Semi-Markov state transition model: 3 mutually exclusive health states: progression-free, progressed disease and death
- All patients enter PF state receiving either osimertinib or placebo
- Overall survival (OS) not an input in model; OS is an output of the model OS estimated using 3 endpoints (time to progression [TTP], progression free survival [PFS] and post-progression survival [PPS])
- Transition probabilities derived from LAURA trial and vary by treatment arm and over time
- Extrapolated time to treatment discontinuation (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	Derived from	Notes
PFS → PD	Time to progression (TTP)	From LAURA BICR-assessed data; fitted parametric curves to TTP data and extrapolated over lifetime horizon
PFS → Dead	Difference between progression free survival (PFS) and TTP	Parametric curves fitted to PFS and TTP data and extrapolated over a lifetime horizon. Calculated as the difference between PFS and TTP curves. Mortality capped at general population rates
PD → Dead	Post-progression survival (PPS)	Based on parametric fit to PPS Kaplan-Meier data from LAURA trial in progressed population

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

Company's model overview (2)

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)

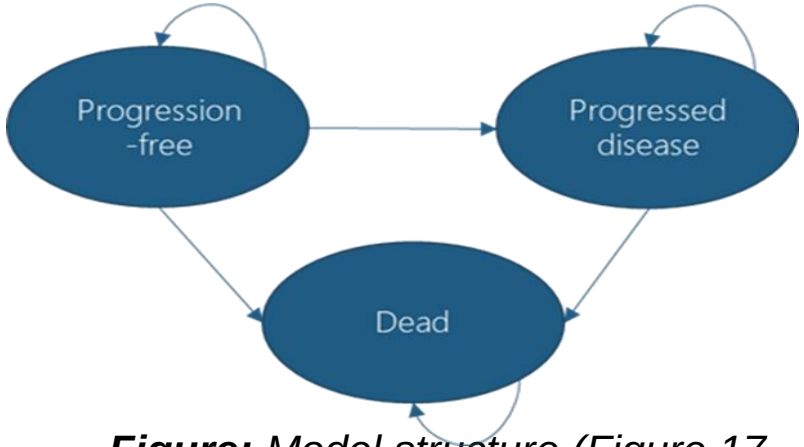

Figure: *Model structure (Figure 17 from CS)*

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

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

ICER Impact: Large

Key Issue 4: Post-progression survival for placebo arm

Background

- LAURA trial PPS data for placebo arm ~21% mature as of Jan 2024
  - 80.6% of people in placebo arm received osimertinib as first subsequent treatment
- Company base case: mean PPS for patients initially treated with BSC is [redacted] months
  - Mean survival in PD health state for BSC is substantially lower than the expected survival of FLAURA trial patients (TA654) treated with 1st line osimertinib in the metastatic setting (56.2 to 60.2 months)
- No formal crossover adjustment applied

Company

- PPS extrapolated using Gompertz distribution, supported by 3 of 5 clinical experts

EAG comments

- Company base case: mean PPS in BSC group is lower than expected for people receiving osimertinib in metastatic NSCLC setting (based on TA654 OS estimates)
- FLAURA trial → informs TA654: more advanced disease (95% metastatic) than LAURA placebo arm post-progression (44%), so first-line metastatic osimertinib survival is a conservative lower bound for BSC PPS
- Weibull distribution gives survival more aligned with TA654 → revised PPS for BSC arm using Weibull
  - Weibull: Longer PPS for BSC arm → narrows incremental benefit → raises ICER significantly
- Emphasised need to align post-progression modelling with plausible treatment sequences, especially given high osimertinib crossover and long assumed osimertinib treatment duration ([redacted] months)

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Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; NSCLC, non small cell lung cancer; PD, progressed disease; PPS, post-progression survival; TA, Technology appraisal

ICER Impact: Large

Key Issue 4: Post-progression survival for placebo arm (2)

Comparison of PPS estimates (adapted from table 24 EAG report)

All estimates are undiscounted

Estimate Type	Source	Osimertinib treatment duration (months)	Survival after discontinuation (months)	Total PPS (months)
Company base case (Gompertz)	LAURA trial / Co. model	[redacted]	[redacted]	[redacted]
EAG base case (Weibull)	EAG revised model	[redacted]	[redacted]	[redacted]
TA654 company base case	TA654 submission	21.96	44.99	66.95
Committee preferred TA654	NICE committee	21.96	34.19 to 38.26	56.15 to 60.22

- Duration adjusted for proportion not receiving osimertinib post-progression
- Survival after discontinuation includes
  - Survival post osimertinib for those treated
  - Total PPS for those not treated
- PPS estimates are influenced by both the survival model used (Gompertz vs Weibull) and assumptions about crossover to osimertinib and disease severity (metastatic vs locally advanced)

See PPS parametric extrapolations for placebo

Is Weibull a more appropriate PPS distribution for BSC than Gompertz? How should PPS be modelled considering large crossover post-progression?

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Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; NSCLC, non small cell lung cancer; PD, progressed disease; PPS, post-progression survival; TA, Technology appraisal

Key Issue 5: Time to progression and progression-free survival

ICER Impact: Moderate

Background
- Company use Weibull distribution for osimertinib TTP and PFS

See PFS parametric extrapolations for osimertinib

Company
- Clinical experts agreed clinically plausible extrapolations + Weibull has relatively good visual & statistical fit

EAG comments
- Weibull may overestimate long-term PFS due to its flattening hazard over time
- Visual inspection of LAURA data suggests progression risk increases after ~28 months, which is inconsistent with Weibull's decreasing hazard function
- 10-year PFS estimate using Weibull is 18.5%, higher than 10–15% range some clinical experts expected
- Weibull may overestimate durability of benefit; exponential distribution provides a plausible alternative, with 10-year PFS estimates falling within the expected 10–15% range (11.6%)
- Hazard of progression appears to change over time in osimertinib arm, suggesting non-proportional hazards
- Few patients (n=28) remain at risk beyond 36 months, increasing extrapolation uncertainty. Long-term progression risks in the osimertinib arm remain uncertain
- Exponential distribution leads to a higher ICER, due to lower QALYs for osimertinib
- Further expert opinion and mature trial data are needed to determine the most appropriate extrapolation

Does Weibull or the exponential distribution best reflect PFS for osimertinib?

Abbreviations: ICER, incremental cost effectiveness ratio; SA, sensitivity analysis; TTP, time to progression; PFS, progression-free survival

ICER Impact: Small

Key Issue 6: PPS for people initially treated with osimertinib

Background and company approach

- PPS data taken from LAURA osimertinib arm short (median follow-up post-progression ~7.5 months)
- Few deaths observed (24/53 progressed) → PPS extrapolation highly uncertain (insufficient events to inform long-term survival curves)
- Company used Gompertz to extrapolate PPS due to increasing hazard over time based on clinical advice
  - Statistical goodness-of-fit similar across exponential, Weibull, Gompertz, gamma, generalized gamma

EAG comments

See PPS parametric extrapolations for osimertinib

- High uncertainty in long-term PPS estimates for osimertinib arm
  - Mixed clinician views, lack of external benchmarks, immature trial data
  - Company's Gompertz-based PPS estimate for osimertinib may be pessimistic and underestimates survival vs BSC → mean survival after progression for osimertinib patients ([redacted] months) is lower compared to patients in BSC arm receiving osimertinib post-progression ([redacted] months)
- Revised approach: switched from Gompertz to exponential distribution to extrapolate PPS for osimertinib;
  - Exponential distribution yields more optimistic PPS ([redacted] months)
  - Used as a sensitivity analysis to reflect plausible upper bound of survival
- Impact on ICER is small, but reflects appropriate structural uncertainty
- PPS: uncertainty: people initially treated with osimertinib are older at progression but have less advanced disease than those who receive osimertinib after progressing on BSC, making comparability uncertain

Which distribution should be used to extrapolate PPS, exponential or Gompertz?

NICE

Abbreviations: ICER, incremental cost effectiveness ratio; PPS, post-progression survival

ICER Impact: Moderate

Key Issue 7: Osimertinib time to treatment discontinuation (1)

Background

- Company used piecewise approach to model osimertinib treatment duration:
  - KM data from LAURA to 36 months → then exponential distribution to extrapolate TTD
- Applied a 10-year stopping rule for osimertinib treatment → stopping rule not in LAURA or MA

Company

- Justified exponential distribution due to small number of people at risk beyond 36 months
- 10-year stopping rule based on clinical advice that indefinite treatment is unlikely

EAG comments

- Piecewise TTD approach caused sustained artificial separation between PFS and TTD curves after 36 months → not supported by LAURA data and inconsistent with a treat-to-progression regimen
- Company approach likely underestimated osimertinib costs in long-term survivors
- Preferred approach:
  - Use Weibull distribution for both PFS and TTD to maintain internal consistency
  - Remove 10-year stopping rule to align with LAURA trial and expected MA

Abbreviations: ICER, incremental cost effectiveness ratio; K-M, Kaplan Meir; MA, marketing authorisation; PFS, Progression free survival; TTD, Time to treatment discontinuation

ICER Impact: Moderate

Key Issue 7: Osimertinib time to treatment discontinuation (2)

[redacted]

EAG approach and comments

- Weibull distribution for PFS & TTD → avoids artificial flattening of TTD curve
  - TTD curve exceeds PFS after 10 years, models cap costs at minimum of PFS/TTD → limited cost impact
  - Removes stop rule → reflects treat-to-progression regimen
  - Graph illustrates improved internal consistency and clinical plausibility without stopping rule
- Removing 10-year rule and using Weibull increases ICER
  - Longer treatment duration + no stop rule → raises ICER, better reflects clinical use and long-term costs for progression-free survivors
- Imposing a stop rule would require assumptions about treatment waning and possible osimertinib retreatment

Is a treatment stopping rule appropriate? How should time to treatment discontinuation be modelled?

Abbreviations: ICER, incremental cost effectiveness ratio; K-M, Kaplan Meir; MA, marketing authorisation; PFS, Progression free survival; TTD, Time to treatment discontinuation

ICER Impact: Moderate

Key Issue 8: Subsequent treatments

Background

- Applied treatment durations and rates to inform modelling of post-progression costs and survival
- Company based subsequent treatment rates on average of 5 clinical expert estimates (not trial data)
- LAURA trial: 80.6% of BSC arm received osimertinib as 1st subsequent treatment, higher than model input
- Company: rechallenge with osimertinib unlikely in NHS. Did not include osimertinib as a subsequent treatment in osimertinib arm. LAURA: 28 people received an EGFR-TKI after discontinuing osimertinib

Company

- Clinician estimates considered more reflective of NHS practice

EAG comments

- Preferable to use trial data i.e. LAURA rather than relying on expert opinion
- Amended model uses trial-based proportions rather than estimates → improving alignment with clinical data and increasing cost estimates for BSC arm → lower ICER

Proportions of model patients receiving first subsequent treatment on progression (from EAG report table 26)

Treatment	Proportion of patients who progressed and receiving ≥1 subsequent treatment (A)		Proportion of patients receiving osimertinib (conditional on progression and receiving ≥1 subsequent treatment) (B)		Proportion of patients who received osimertinib as first subsequent treatment (A x B)	
	Company base case	EAG revision	Company base case	EAG revision	Company base case	EAG revision
Osimertinib	[redacted]	79.3%	-	-	-	-
BSC	[redacted]	91.9%	[redacted]	87.7%	[redacted]	80.6%

How should post-progression be modelled? Should trial data inform post-progression treatment rates?

Abbreviations: ICER, incremental cost effectiveness ratio; K-M, Kaplan Meir; MA, marketing authorisation; PFS, Progression free survival; TTD, Time to treatment discontinuation

ICER Impact: Small

Key Issue 9: Health state utility values (HSUVs)

Background

- Company progression-free HSUV exceeded general population utility values
- Company base case
  - PF utility value: [redacted] taken from LAURA trial EQ-5D-5L data mapped to EQ-5D-3L
  - PD utility value: (0.794) FLAURA trial PF baseline used in TA654 (people with metastatic disease)

EAG comments and NICE technical team

- PF utility value exceeds general population
  - PF HSUV higher than age- and sex-matched EQ-5D-3L general population: 0.831
  - Unlikely people with cancer have better HRQoL than the general public
- PD utility value may overestimate HRQoL after progression
  - LAURA trial PD data = small sample (n=102), doesn't reflect further HRQoL decline in progressive disease. No split between early vs. late PD stages → model oversimplifies post-progression experience
- EAG Revisions:
  - PF = 0.831 (age- and sex-adjusted general population average): ICER increases
  - PD = 0.725, average of PF (0.794) and PD (0.704, 0.68) TA654 HSUVs: ICER decreases
- NICE technical team scenario analysis showed further reducing the PF (0.804 from TA1060) increased the ICER, while reducing the PD (0.674 from TA1060) decreased the ICER
- Future modelling may consider separate early/late PD states to better capture declining HRQoL

TA1060: Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer

Abbreviations: HRQoL, health-related quality of life; HSUV, health state utility value; ICER, incremental cost effectiveness ratio; PD, progressed disease; PF, progression-free

What approach should be used for health state utilities?

Summary of company and EAG base case assumptions

Table: Assumptions in company and EAG base case

Assumption	Company	EAG
	Base case	Base case
Time horizon	• 38.6 years	• Same as company
Comparator	• Best supportive care (BSC) only	• Same as company
Survival modelling	• PPS using Gompertz distribution • PFS and TTP extrapolated using Weibull • OS not directly modelled due to immaturity	• PPS Weibull distribution for BSC arm, Gompertz for osimertinib • OS = alternative post-progression survival assumptions to account for crossover effects
Subsequent treatment rates	• Based on 5 clinician average estimates (lower osimertinib use post-progression)	• Revised to use LAURA trial proportions (e.g., 87.7% received osimertinib in placebo arm)
Time to treatment discontinuation	• KM data up to 36 months, exponential thereafter • Intervention osimertinib stops at 10 years	• Same distribution as PFS (Weibull) from model start • Removed 10-year stopping rule
Utilities	• PF: from LAURA trial • PD: from FLAURA trial	• PF: adjusted to align with general UK population norms • PD: from FLAURA trial
Health state costs	• Resource use based on UK practice and expert input	• Same as company

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

Should a managed access recommendation be made? If so, for what duration of data collection is needed to address the key uncertainties, given the maximum duration of managed access is 5 years?

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

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**

NICE National Institute for Health and Care Excellence

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 EAG's ICERs are 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

NICE National Institute for Health and Care Excellence

PPS parametric extrapolations for placebo

See Key Issue 4: Post-progression survival for placebo arm

Observed and estimated PPS rates and AIC/BIC of survival models for placebo

Distribution	Weibull	Gompertz
AIC	[redacted]	[redacted]
AIC rank	[redacted]	[redacted]
BIC	[redacted]	[redacted]
BIC rank	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3 years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
15 years	[redacted]	[redacted]

Adapted from table 36 from company submission

Adapted from figure 32 from company submission

- Wide variation in the long-term estimates of PPS due to data immaturity.
- Company base: used Gompertz, considered distribution more closely aligns with the smoothed hazard profile
- EAG base: used Weibull, considered similar statistical fit to the Gompertz and distribution was considered plausible by 3 clinicians consulted by the company

Abbreviations; AIC, Akaike information criterion; BIC, Bayesian information criterion, PPS; post progression survival

PFS parametric extrapolations for osimertinib

See Key Issue 5: Time to progression and progression-free survival

- Wide variation in the long-term estimates of PFS due to data immaturity.
- EAG: between 28 to 36 months, no distribution reflects change in the within trial hazard of progression
- Exponential: most conservative estimate in range suggested by clinicians (10-15%)
- AIC and BIC scores relatively consistent across all distributions

Observed and estimated osimertinib progression-free survival rates

Distribution	AIC score (difference from highest ranked distribution)	BIC score (difference from highest ranked distribution)	Progression-free survival		
			3-year	5-year	10-year
LAURA trial	-	-	58.36%	44.79%[a]	-
Weibull	573.4 (6.4)	579.3 (5.5)	53.81%	38.90%	18.49%
Exponential	573.9 (6.9)	576.9 (3.1)	52.32%	34.18%	11.55%

Adapted from table 25, EAG report. [a] Only 1 patient at risk therefore Kaplan-Meier estimate may be unreliable

Abbreviations; AIC, Akaike information criterion; BIC, Bayesian information criterion, PFS; progression free survival

PPS parametric extrapolations for osimertinib

See Key Issue 6: Post-progression survival for osimertinib

Observed and estimated PPS rates and AIC/BIC of survival models for osimertinib

Distribution	Gompertz	Exponential
AIC	[redacted]	[redacted]
AIC rank	[redacted]	[redacted]
BIC	[redacted]	[redacted]
BIC rank	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
3 years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
15 years	[redacted]	[redacted]

Adapted from table 35 from company submission

Adapted from figure 31 from company submission

- Wide variation in the long-term estimates of PPS due to data immaturity.
- Company base: used Gompertz, considered distribution more closely aligns with the smoothed hazard profile
- EAG provided scenario analysis using exponential distribution

Abbreviations; AIC, Akaike information criterion; BIC, Bayesian information criterion, PPS; post progression survival