Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from AstraZeneca
2. **Company summary of information for patients (SIP)** from AstraZeneca
3. **Company additional evidence – updated OS analyses** from AstraZeneca
4. **Clarification questions and company responses**
5. **Patient group, professional group and NHS organisation submissions** from:
   a. EGFR Positive
   b. Roy Castle Lung Cancer Foundation
   c. Association of Respiratory Nurse Specialists
   d. British Thoracic Oncology Group
6. **Expert personal perspectives** from:
   a. Dr Elizabeth Toy – clinical expert, nominated by AstraZeneca
   b. Nina Kale – patient expert, nominated by EGFR Positive
7. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group
   a. External Assessment Report
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   a. Factual accuracy check
   b. EAG additional clarification questions post-factual accuracy check and company responses
9. **Managed access feasibility assessment**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted

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Single technology appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced or unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Document B

Company evidence submission

January 2025

File name	Version	Contains confidential information	Date
ID6223 Osimertinib LAURA DocB 15Jan25_redacted	**1.0**	**Yes**	**15th January 2025**

Contents

Tables and figures

Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BIM	Budget impact model
BNF	British National Formulary
BoR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CCRT	Concurrent chemoradiation
CDF	Cancer Drugs Fund
CEM	Cost-effectiveness model
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRT	Chemoradiation
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
DARE	Database of Abstracts of Reviews of Effects
DCO	Data cut-off
DCR	Disease control rate
DF	Disease free
DM	Distant metastasis
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	External Assessment Group
ECG	Electrocardiogram
EFR	Evaluable for response
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth-factor receptor mutation
EGFR-TKI	Epidermal growth-factor receptor tyrosine kinase inhibitor
EMA	European Medicines Agency
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire

EORTC-QLQ-L13	European Organisation for Research and Treatment of Cancer 13-item lung cancer module
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	Food and Drug Administration
GP	General practitioner
HCRU	Health Care Resource Utilisation
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan–Meier
LYG	Life years gained
MMRM	Mixed models for repeated measures
MRI	Magnetic resonance imaging
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NHB	Net health benefit
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not recorded
NSCLC	Non-small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PBO	Placebo
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PF	Progression free
PFS	Progression-free survival
PFS2	Time to second progression
PHA	Proportional hazards assumption
PPS	Post-progression survival

PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QD	Every day
QoL	Quality of life
SAE	Serious adverse event
SAS	Safety analysis set
SCRT	Subsequent chemoradiation
SD	Stable disease
SLR	Systematic literature review
SoC	Standard of care
SRS	Stereotactic radiosurgery
STM	State transition model
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TFST	Time to first subsequent treatment
TP	Transition probability
TSD	Technical support document
TSST	Time to second subsequent treatment
TTD	Time to treatment discontinuation
TTDM	Time to death or distant metastases
TTP	Time to progression
UK	United Kingdom
VAS	Visual Analogue Scale
WBRT	Whole brain radiotherapy
WHO	World Health Organization
wtEGFR	Wild-type epidermal growth-factor receptor
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

- **Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) which has been compared with best supportive care (BSC) for the treatment of adult patients with locally advanced, unresectable (stage III) 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 (CRT)**
  - Osimertinib is an oral therapy and is currently reimbursed for:[1-3]
    - ◊ first-line treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor mutation (EGFRm) positive NSCLC
    - ◊ patients with T790M mutation-positive EGFR after first-line treatment with an EGFR-TKI
    - ◊ for the adjuvant treatment of adult patients with EGFRm NSCLC after complete tumour resection
- **There are no targeted treatments available for patients with locally advanced, unresectable EGFRm NSCLC whose disease has not progressed during or following CRT and patients are at high risk of disease progression to the metastatic phase, highlighting a clear unmet need for targeted, efficacious and well-tolerated treatment option for these patients**
  - There are no therapies recommended by National Institute for Health and Care Excellence (NICE) specifically targeting EGFRm expressing NSCLC tumours following CRT, where there is a high clinical unmet need
  - Approximately 70% of patients with unresectable EGFRm NSCLC develop recurrence or metastases within 2 years of receiving CRT[4-6]
  - Metastatic disease is associated with substantially lower survival than advanced disease (5-year survival of 25% in Stage III vs 9% in metastatic disease)[7]
  - Patients with EGFRm NSCLC have nearly double the risk of developing brain metastases compared with those with wild-type EGFR (wtEGFR) (70% vs 38%), which is a key predictor of mortality and is associated with a heavy symptom and quality of life burden[8]
  - The current standard of care (SoC) for EGFRm patients is BSC consisting of active monitoring only.[9] There are no effective active interventions available for EGFRm patients to delay recurrence or progression to metastatic disease, including central nervous system (CNS) metastasis
- **Osimertinib has demonstrated an unprecedented progression-free survival (PFS) benefit and delay in CNS disease progression versus placebo among EGFRm-positive NSCLC patients after CRT in the LAURA trial with no new safety concerns[10]**
  - Osimertinib demonstrated a clinically and statistically significant 84% reduction in the risk of disease progression or death (Hazard ratio [HR]: 0.16 [95% CI: 0.10,

0.24]; p<0.001) and an unprecedented 33.6-month improvement in median PFS compared with placebo[10]
  - A nominally statistically significant and clinically meaningful 83% reduction in the risk of CNS disease progression or death was observed with osimertinib versus placebo (HR: 0.17 [95% CI: 0.09, 0.32], p<0.001[10]
  - Osimertinib has a tolerable safety profile, results in no clinically meaningful deterioration in patient-reported outcomes (PROs) from baseline,[10] and is already an established and familiar treatment for physicians across other EGFRm NSCLC stages[11]

- **Osimertinib is considered to be an innovative, practice changing medicine for treatment of locally advanced, unresectable EGFRm-positive NSCLC after CRT[12]**
  - Due to the innovative nature of this indication and unprecedented magnitude of benefit observed in the trial, osimertinib for the treatment of adult patients with locally advanced unresectable[10] EGFRm NSCLC after CRT was granted Breakthrough Therapy Designation and has been granted FDA[13] and EMA[14] approval for this indication
  - UK marketing authorisation is expected in [redacted]
  - UK clinical experts have stated that the findings from the LAURA trial are practice changing and provide a strong evidence base to support the integration of osimertinib in treatment protocols for EGFRm NSCLC patients post-CRT[15]

- **Osimertinib represents an important advancement in the management of locally advanced unresectable EGFRm NSCLC for patients whose disease has not progressed during or following CRT, addressing a substantial unmet need for patients who currently have no targeted and efficacious treatment options that can delay progression to metastatic disease**

B.1.1 Decision problem

The submission covers the technology's full anticipated marketing authorisation for this indication:

[redacted]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Intervention	Osimertinib	As per NICE scope	
Population	Adults with EGFR mutation-positive (exon 19 deletion or L858R, either alone or in combination with other EGFR mutations) locally advanced unresectable NSCLC whose disease has not progressed after platinum based chemoradiation	As per NICE scope	
Comparator(s)	Durvalumab (for people who had concurrent chemoradiation therapy and have PD-L1 positive NSCLC) Best supportive care	Best supportive care	Best supportive care, consisting of active monitoring, represents the current SoC for patients with EGFRm locally advanced or unresectable NSCLC after CRT. Durvalumab is recommended by NICE TA798 for maintenance treatment of unresectable NSCLC after CRT,[16] but it is not recommended in current ESMO expert consensus statements for this group of patients due to uncertain efficacy.[17] Clinical expert feedback confirmed that durvalumab is not used post-CRT for patients with EGFRm in UK clinical practice. Durvalumab has therefore been excluded as a comparator.[15]
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • disease free survival	As per scope with the exception of disease-free survival	Disease free survival (DFS) is not an appropriate outcome for this appraisal. This outcome is typically used in clinical trials of adjuvant therapies (therapies used after resection of a tumour). The LAURA trial studied osimertinib as a maintenance therapy in locally advanced, unresectable

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• response rates • adverse effects of treatment • health-related quality of life		NSCLC and did not collect DFS. Progression-free survival was the primary outcome of this trial used to assess the efficacy of osimertinib, as maintenance therapy, compared with placebo.[18, 19]
Subgroups to be considered	If the evidence allows then the following subgroups will be considered: • people who had concurrent or sequential chemoradiation therapy • PD-L1 expression • disease stage • newly diagnosed or recurrent NSCLC (including post surgery recurrence) • treatments had at previous stages (if any) • type of EGFR mutation	Pre-specified subgroups were included in the pivotal trial (LAURA) and the relevant efficacy data are presented in this submission (Section B.2.6.1). These subgroups were based on demographics, smoking status, prior CRT strategy (CCRT vs SCRT), disease stage prior to CRT, central plasma ctDNA EGFR (Ex19del or L858R) mutation status at screening, tissue EGFR mutation at screening, and response to prior CRT. No subgroup analyses are presented for the economic evaluation because a consistent treatment effect was observed, and therefore the analysis is based on the full population.	PD-L1 expression, newly diagnosed or recurrent NSCLC, and treatments had at previous stages were not pre-specified subgroups of the LAURA trial

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission are provided in Table 2.

Table 2: Technology being evaluated

UK approved name and brand name	Osimertinib (TAGRISSO®)
Mechanism of action	Osimertinib provides highly selective and irreversible inhibition of activating sensitising EGFRm and activating resistance mutation T790M, without affecting the activity of wild-type EGFR. Inhibition of phosphorylation of EGFR and downstream signalling leads to tumour growth inhibition and also induces cell cycle arrest.
Marketing authorisation/CE mark status	MHRA marketing authorisation is expected in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	***Indication covered in this submission:*** Osimertinib is expected to be indicated [redacted]. ***Existing relevant indications for osimertinib:*** Osimertinib as monotherapy is indicated for:[11] • the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations • the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations • the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC Osimertinib is indicated in combination with: • pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations
Method of administration and dosage	Osimertinib is available as 40 mg or 80 mg oral tablets. The recommended dose is 80 mg once a day.
Additional tests or investigations	EGFR mutation status should be determined by a validated test method, using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample. NICE recommends testing for EGFRm in people with previously untreated, locally advanced/metastatic NSCLC.[20]
List price and average cost of a course of treatment	Osimertinib is available at a list price of £5,770 per 30 tablets (40 mg or 80 mg).[21]
Patient access scheme (if applicable)	[redacted].

B.1.3 Health condition and position of the technology in the treatment pathway

- **Non-small cell lung cancer (NSCLC) is a highly prevalent form of cancer, accounting for 58% of all lung cancer cases[22] and is the number one cause of cancer deaths in the UK[23]**
- **Epidermal growth factor receptor mutations (EGFRm) are found in 10% of all NSCLC cases[22]**
  - Exon 19 deletions and L858R point mutations account for around 90% of EGFRm cases[12, 13]
  - Epidermal growth factor receptor mutations are more common in never smokers than past or current smokers[24]
- **Approximately 21% of NSCLC cases are diagnosed with locally advanced disease[22]**
  - An estimated 82% of locally advanced NSCLC cases are unresectable[22] and around 60% of patients with locally advanced NSCLC receive CRT[22]
- **The SoC for patients with locally advanced unresectable EGFRm NSCLC is CRT followed by BSC, however following treatment, patients are at high risk of progressing to metastatic disease due to lack of targeted treatment options following CRT[4-6]**
  - Patients with EGFRm NSCLC have shorter or similar PFS following CRT than patients with wtEGFR tumours[25]
  - Approximately 70% of patients with locally advanced unresectable EGFRm NSCLC develop recurrence or metastasis within 2 years of CRT[4-6]
  - Over 50% of EGFRm NSCLC patients develop distant metastases upon disease progression[4-6]
- **Progression to metastatic NSCLC is associated with a substantially poorer survival, an increase in disease symptoms, and a significant reduction in quality of life (QoL) compared with advanced disease**
  - In England 5-year survival rates decrease from 24.9% with locally advanced disease to 8.8% with metastatic disease[7]
  - Progression from locally advanced to metastatic disease is associated with an increase in symptom burden including weakness, pain, seizures, and other neurological symptoms if CNS metastases are present[26-29]
  - Patients with EGFRm NSCLC are at nearly double the risk of developing CNS metastases (70% vs 38%) compared with wild-type EGFR (wtEGFR) NSCLC patients[8]
  - Patients experience a substantial decrease in QoL with EQ-5D scores reported to fall from 0.7 to 0.58 between locally advanced and metastatic disease[30]
- **With the lack of meaningful innovation for EGFRm patients following CRT, there is a substantial unmet need for a targeted treatment option that can delay progression to metastatic disease and improve patient outcomes**

- Standard of care for EGFRm patients in the UK therefore consists of BSC (active monitoring only), which is associated with poor outcomes[15]
- Durvalumab is the SoC for treatment after concurrent CRT for NSCLC patients whose tumours express PD-L1,[16] however current European Society for Medical Oncology (ESMO) expert consensus statements do not recommend the use of durvalumab in patients with EGFRm NSCLC due to uncertain benefit and greater toxicity[31, 32]
- UK clinical experts consulted as part of an advisory board stated that durvalumab is not routinely prescribed for locally advanced, unresectable EGFRm NSCLC patients[15]

- **Osimertinib is expected to be the first treatment which can significantly delay progression to metastatic disease for advanced unresectable EGFRm NSCLC patients whose disease has not progressed after platinum-based CRT, representing a substantial innovation in this treatment setting**

B.1.3.1 Lung cancer overview

Lung cancer is the third most common cancer in the UK, with 49,229 cases diagnosed each year, and is the number one cause of cancer deaths, accounting for 21% of all cancer deaths between 2017-2019 in the UK.[33] Non-small cell lung cancer is the most prevalent form of lung cancer in England and Wales, accounting for 58% of all lung cancers.[22, 23]

Among the mutations observed in NSCLC, EGFR mutations are a common type. They are found in 10% of NSCLC patients,[34] of which exon 19 deletions and L858R point mutations account for around 90% of cases. [35, 36] The exact cause of EGFRm lung cancer is not fully understood, and EGFRm driven NSCLC is more common in patients who have never smoked than in current or previous smokers.[37] It has been hypothesised that exposure to other carcinogens (e.g. air pollution) causes genetic mutations and modifications in protein synthesis, resulting in the abnormal growth of cells in the lung.[38, 39] Epidermal growth factor receptor mutations are associated with more aggressive disease progression than tumours that do not harbour EGFRm[40], with patients having nearly double the risk of developing brain metastases (70% vs 38%) compared with wtEGFR NSCLC patients.[8]

Despite advances made in screening, early detection, and staging, the majority of lung cancer patients present at an advanced stage, with approximately 21% of NSCLC cases diagnosed at Stage III (locally advanced).[22]

The SoC for locally advanced unresectable NSCLC is CRT and treatment is given with curative intent, as stated by UK clinical experts consulted as part of an advisory board.[15] However, 70% of patients with EGFRm experience relapse or progression to metastatic disease within 2 years of treatment. Following CRT, patients receive BSC (consisting of active monitoring); there are no targeted therapies recommended by NICE for patients with EGFRm expressing NSCLC tumours to delay recurrence or progression to metastatic disease. Patients who progress to metastatic disease have dramatically reduced 5-year survival rates (24.9% vs 8.8%) compared with patients with locally advanced disease,[7] and experience poorer quality of life.[27]

B.1.3.1.1 Epidemiology

There are approximately 36,866 cases of lung cancer diagnosed in England each year,[22] with NSCLC accounting for 58% of cases.[22] Early-stage NSCLC is often asymptomatic,[41] and approximately 21% of patients present with locally advanced (stage III) disease.[22] The majority (74%) of cases are non-squamous type[34] and more than 80% of advanced NSCLC patients have unresectable disease.[22] EGFR mutations are found in approximately 10% of NSCLC patients,[34] with exon 19 deletions and L858R point mutations accounting for around 90% of cases.[35, 36] The incidence of patients with EGFRm (exon 19 deletions or exon 21 [L858R] substitution mutations) positive NSCLC diagnosed with locally advanced unresectable disease and who undergo CRT and who will be eligible for treatment with osimertinib in England is estimated to be approximately 150 patients per year.

B.1.3.1.1.1 Life expectancy

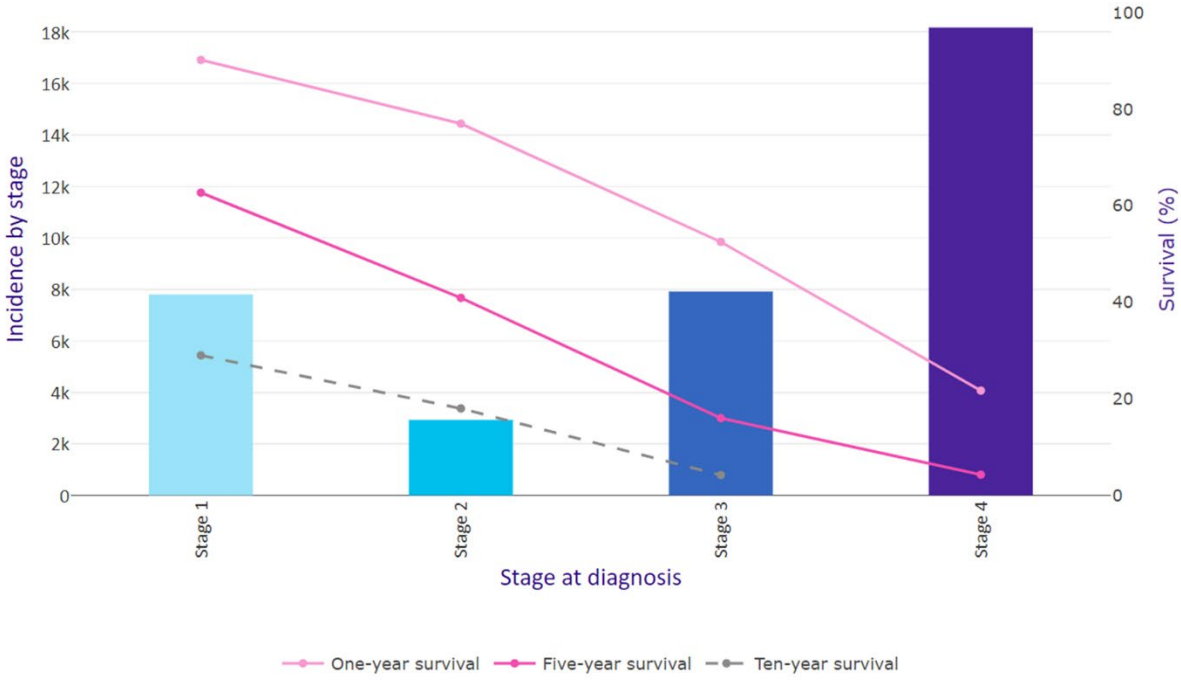
Following treatment with CRT approximately 70% of patients with locally advanced unresectable EGFRm NSCLC develop recurrence or metastasis within 2 years.[4-6] In England, five-year lung cancer survival rates decrease dramatically with disease stage (Figure 1), with patients diagnosed at Stage III (locally advanced) having a 5-year overall survival rate of ~25%, compared with ~9% for patients diagnosed at Stage IV (metastatic) (Table 3).[7]

Table 3: Lung cancer survival in England†

Stage	5-year net survival, %	5-year overall survival, %
I	62.7	67.8
II	40.9	49.1
III	16.0	24.9
IV	4.3	8.8

† 5-year survival is based on adult lung cancer cases diagnosed in 2016 and followed to 2021.
Source: NHS England 2023.[7]

Figure 1: Incidence and survival of lung cancer cases by stage at diagnosis, England 2016-2020



Source: CRUK.[33]

Patients with EGFRm are at an increased risk of developing CNS metastases than patients with wtEGFR,[8] which further impact survival outcomes. Central nervous system metastases are associated with median OS of 4–9 months with chemotherapy and 7 months with whole brain radiation therapy.[42, 43] Untreated patients with CNS metastases have a median survival of just 2 months.[42, 44]

B.1.3.1.2 Burden of disease

B.1.3.1.2.1 Clinical burden

Symptoms of NSCLC typically develop once the cancer becomes more advanced and include a persistent cough, coughing up blood, persistent breathlessness,

unexplained tiredness and weight loss, repeated chest infections, ascites, jaundice, and pain on breathing or coughing.[45] [46-48] Patients with locally advanced unresectable EGFRm NSCLC are at high risk of progression, with 70% of patients developing recurrence or metastasis within 2 years of receiving CRT, with CNS being a common metastatic site for NSCLC.[4-6, 8, 49, 50]

In patients with EGFRm NSCLC, CNS and bone metastases are associated with a higher frequency of seizures, speech problems, focal neurological deficits, vision disorder, fatigue, nausea, headaches, problems with memory, altered mental status, bone pain, broken bones, weakness in extremities, hypercalcaemia, and mobility issues.[29, 48] Furthermore, UK patients diagnosed with brain metastases have their driving licenses suspended, leading to loss of independence.[51] The decline in neurological and cognitive function, complex symptoms, and limited life expectancy, highlights an urgent need for these patients to delay CNS metastasis as long as possible.[29, 46-48, 52, 53]

B.1.3.1.2.2 QoL burden

Patients with NSCLC experience poorer physical health and quality of life in the advanced stages of disease, which worsens on progression to metastatic disease.[27] In a prospective, multi-country, cross-sectional analysis of patients with Stage IIIB or IV NSCLC, a decline in health-related quality of life (HRQoL) (as measured by EQ-5D index values) was observed for patients with progressive disease vs those who remained progression free (0.58 vs 0.70, respectively).[30] The progression to metastatic disease and increasing symptom burden is associated with an increased psychological burden for patients, including death anxiety and demoralisation.[54] Furthermore, patients with brain metastases experience a high symptom burden which translates into a clinically meaningful deterioration in HRQoL compared with patients without brain metastases ($p<0.0001$).[55]

Due to the high burden of symptoms experienced in advanced and metastatic disease, patients with NSCLC may require physical or emotional support from caregivers.[56] The burden of care can negatively affect the caregivers ability to work and can impact them physically, emotionally, and financially.[57, 58]

B.1.3.1.2.3 Economic burden

Non-small cell lung cancer represents a significant economic burden, costing an estimated £2.4 billion to the UK economy in 2012.[59] While in the early stages of disease the main costs are incurred by surgery, in the more advanced stages medical therapy, radiotherapy, treatment for progression, as well as supportive care become more important.[60] Furthermore, the total costs of cancer are predicted to rise globally over the next 30 years to $25 trillion, with lung, tracheal and bronchial cancers predicted to be the most costly. Estimations suggest that lung, tracheal and bronchial cancers will account for 15.4% of the total global economic cost of cancer by 2050.[61]

B.1.3.2 Current clinical pathway of care

There are no targeted, efficacious active treatment options available for patients with locally advanced unresectable EGFRm NSCLC following CRT in the UK, and the current SoC for these patients is BSC (consisting of active monitoring only).[9]

National Institute for Health and Care Excellence guidance (TA798) recommends durvalumab treatment for people whose NSCLC is PD-L1 positive and has not progressed after concurrent platinum-based chemoradiation.[16] However durvalumab has not demonstrated statistically significant efficacy in patients with EGFRm NSCLC (Section B.1.3.3),[62, 63] and is associated with a higher frequency of severe immune-related adverse events (AEs) in this patient population.[32] It is therefore not recommended for use in patients with EGFRm NSCLC in current ESMO expert consensus statements.[32] UK clinical experts consulted as part of an advisory board stated that they therefore do not use durvalumab following CRT for EGFRm patients.[15]

B.1.3.3 Unmet need in the current clinical care pathway

As described above, there are currently no targeted, efficacious therapies recommended by NICE for patients with EGFRm expressing NSCLC tumours after platinum-based CRT. Despite NICE recommendation of TA798,[16] post-hoc clinical trial data from the Phase 3 PACIFIC study showed limited clinical effectiveness of durvalumab in patients with EGFRm NSCLC.[16] In the PACIFIC study, pre-specified subgroup analysis revealed that a total of 35 patients (4.9%) tested positive for

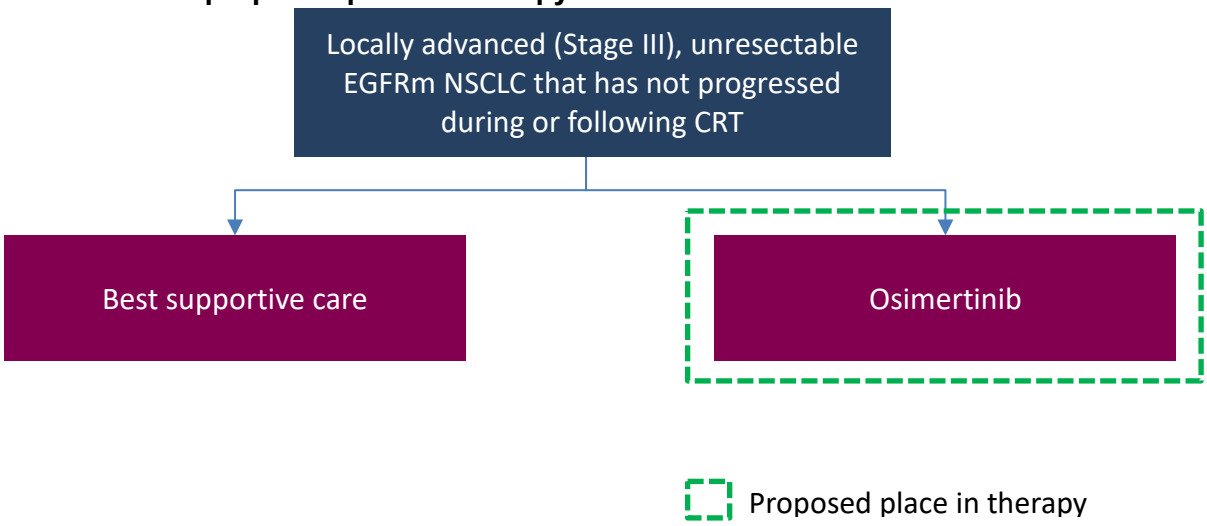
EGFRm across the durvalumab and placebo arms; PFS and overall survival (OS) outcomes with durvalumab were similar to placebo for patients with EGFRm tumours, with wide confidence intervals (CIs) (median PFS: 11.2 months versus 10.9 months; HR: 0.91; 95% CI: 0.39, 2.13 and median OS: 46.8 months versus 43.0 months; HR: 1.02; 95% CI: 0.39, 2.63).[31, 64] Based on the available evidence, the latest European Society for Medical Oncology (ESMO) expert consensus statements (2022) recommend against the use of durvalumab treatment after CRT for patients with advanced EGFRm NSCLC.[32] UK clinical experts consulted as part of an advisory board have stated that durvalumab is not routinely offered to patients with unresectable locally advanced EGFRm NSCLC in the UK.[15]

Clinical experts stated that patients with EGFRm NSCLC in the UK receive BSC (consisting of active monitoring only) after CRT,[15] with no additional interventions available to delay recurrence or progression to metastatic disease.[9] Post-CRT treatment, patients with locally advanced unresectable EGFRm NSCLC have a significantly higher recurrence and distant metastasis rates compared with patients with wtEGFR disease[50] with approximately 70% of EGFRm patients developing recurrence or metastasis within 2 years.[4-6] Over half of these patients will develop - metastasis upon progression (30% local recurrence, 40% distant metastasis).[4-6] Patients with EGFRm NSCLC are at nearly double the risk of developing CNS metastases (70% versus 38%) compared with wtEGFR NSCLC patients.[8] Progression to metastatic disease is associated with a substantial reduction in QoL and worse 5 year survival (from 25% in locally advanced disease to 9% in metastatic disease).[33] There is therefore a substantial unmet need for a targeted and efficacious treatment in this patient population in order to delay disease progression and maintain quality of life.

B.1.3.4 Osimertinib place in therapy

An overview of the current clinical care pathway for patients with locally advanced unresectable EGFRm NSCLC with the proposed place in therapy for osimertinib presented in Figure 2.

Figure 2: Current treatment pathway for locally advanced unresectable EGFRm NSCLC with a proposed place in therapy for osimertinib



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

As there are currently no targeted treatments for this patient population,[25] osimertinib treatment represents the first opportunity to prolong PFS in patients with EGFRm NSCLC, with no meaningful deterioration in QoL, and delay the development of CNS metastases.

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

- first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations (TA654)[1]
- treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC (TA653)[2]
- for the adjuvant treatment of adult patients with EGFRm NSCLC after complete tumour resection

The current appraisal expands this population to include [redacted].

B.1.3.5 Clinical guidelines

Latest European Society for Medical Oncology (2022) and National Comprehensive Cancer Network (NCCN) guidelines (2024) for management of locally advanced unresectable NSCLC state the following:

- European Society for Medical Oncology expert consensus statements do not recommend immune checkpoint inhibitor (ICI) therapy in EGFRm patients post-CRT[32]
- National Comprehensive Cancer Network guidelines[65] and literature evidence suggest EGFRm status precedes PD-L1 mutation status in treatment prioritisation
  - osimertinib is recommended for treatment of patients with unresectable EGFRm NSCLC post-CRT[65, 66]

B.1.4 Equality considerations

Use of osimertinib in NSCLC is not expected to raise any equality issues.

B.2 Clinical effectiveness

- **The evidence from the LAURA trial shows that osimertinib demonstrates a significant, unprecedented improvement in PFS. This addresses a substantial unmet need for EGFRm patients who currently have no targeted treatment options following CRT that delay progression to metastatic disease and is considered by UK clinical experts to be practice changing**
  - The clinical evidence for osimertinib is derived from LAURA, a global, Phase III, double-blind, placebo-controlled, randomised study[10, 67, 68]
  - LAURA assessed the efficacy and safety of osimertinib compared with placebo in patients with locally advanced unresectable EGFRm NSCLC without progression on or after CRT
- **For the primary efficacy outcome, PFS per Blinded Independent Central Review (BICR), osimertinib demonstrated a clinically and statistically significant 84% reduction in the risk of disease progression or death (HR: 0.16 [95% CI: 0.10, 0.24]; p<0.001) and an unprecedented 33.6-month improvement in median PFS compared with placebo**
  - Early separation of the Kaplan-Meier (KM) curves was seen from 8 weeks post-randomisation and this was sustained over the follow-up period
  - The PFS benefit of osimertinib was consistently observed across all pre-defined subgroups
  - The [redacted], supporting the long-term benefits of osimertinib
- **A nominally statistically significant and clinically meaningful 83% reduction in the risk of CNS disease progression or death was observed with osimertinib versus placebo (HR: 0.17 [95% CI: 0.09, 0.32], p<0.001)**
  - A clinically meaningful improvement in time to death or distant metastases (TTDM) was observed following treatment with osimertinib versus placebo (HR=0.21, nominal p<0.001)
- **An initial positive trend in overall survival was observed with osimertinib versus placebo despite only 19.9% data maturity (HR: 0.81 [95% CI: 0.42, 1.56]; p=0.530)**
  - The OS results should be interpreted in the context of low number of events and substantial crossover, with 80.6% of patients in the placebo arm receiving osimertinib after confirmed disease progression due to the osimertinib being the standard of care in the treatment of first-line metastatic NSCLC
  - A final OS analysis is planned when data are 60% mature expected in [redacted])
- **The efficacy benefits of osimertinib were delivered with no clinically meaningful deterioration in HRQoL**
- [redacted]

[redacted]

- **Osimertinib demonstrated a tolerable safety profile which is consistent with its known profile across other EGFRm NSCLC indications**
  - In both treatment arms, most AEs reported were mild or moderate in severity
  - Adverse events leading to treatment discontinuation were low with osimertinib (12.6%) and placebo (5.5%)

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant clinical data assessing the clinical effectiveness and safety of treatments, including osimertinib and relevant comparators for the treatment of adult patients with unresectable locally advanced EGFRm NSCLC following CRT treatment. The SLR was conducted in July 2023 and updated in August 2024.

An overview of the methodology, including search strategy, PRISMA flow diagram, list of included studies and list of excluded studies at full paper review is provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified one relevant RCT reporting on the clinical effectiveness of osimertinib, LAURA (Table 4).

Table 4: Clinical effectiveness evidence

Study	LAURA
Study design	Phase 3, double-blind, placebo-controlled, randomised study
Population	Patients with EGFRm (exon 19 deletion or L858R mutation) with locally advanced unresectable NSCLC who have not progressed during or after CRT
Intervention(s)	Osimertinib
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes

Study	LAURA
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	• **Overall survival** • **Progression-free survival** • Central nervous system progression-free survival • Response rates • **Time to treatment discontinuation** • **Adverse events Health-related quality of life**
All other reported outcomes	• Time to second progression • Time to first subsequent treatment • Time to second subsequent treatment

Abbreviations: CRT, chemoradiotherapy; EGFRm, epidermal growth factor receptor mutation positive; exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; LAURA, A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer; NA, not applicable; NSCLC, non-small cell lung cancer.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

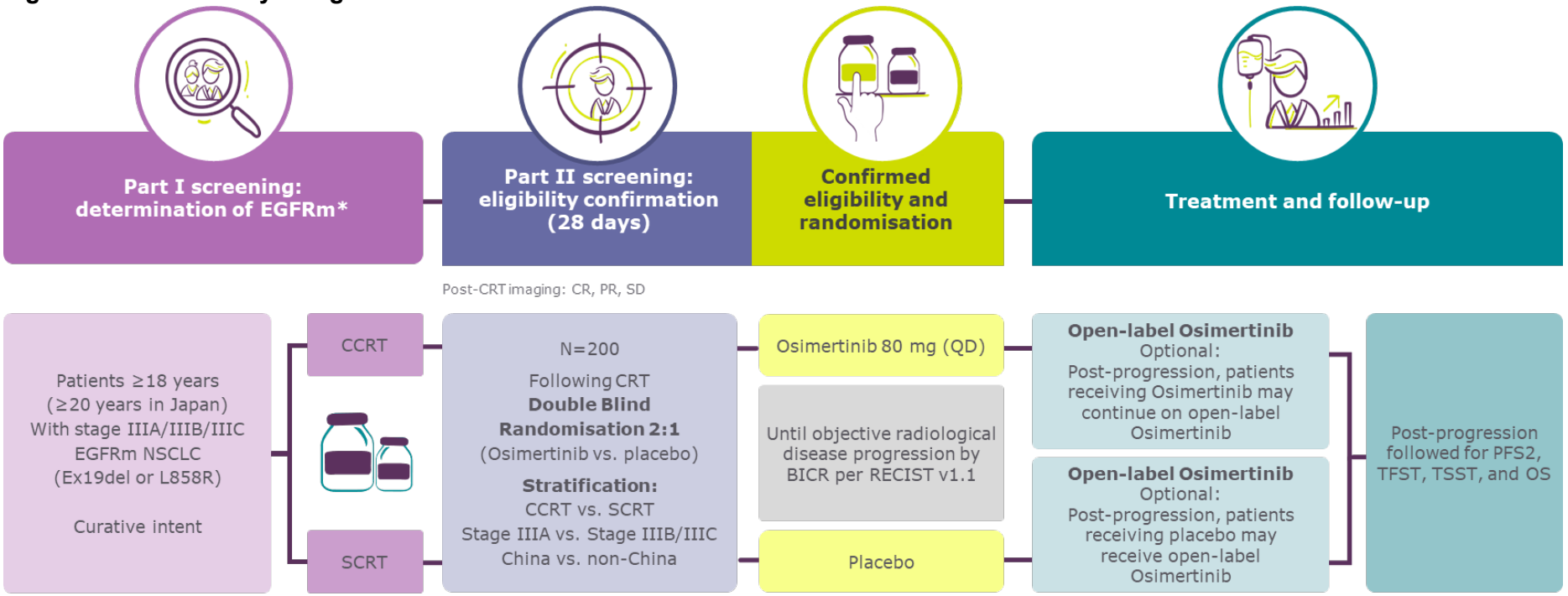
B.2.3.1 Summary of trial methodology – LAURA (Study D5160C00048)

LAURA is an ongoing, global, Phase 3, double-blind, placebo-controlled, randomised study to assess the efficacy and safety of osimertinib treatment for patients with EGFR mutation-positive (Ex19del and/or L858R) NSCLC, whose disease has not progressed during or following definitive platinum-based CRT. The trial design for LAURA is summarised in Figure 3.

The methodology and results from LAURA are drawn from the clinical study protocol,[69] clinical study report (CSR)[10] and publications.[67, 68, 70]

The methodology for LAURA is presented in Table 5. Details of the study inclusion and exclusion criteria are presented in Table 6.

Figure 3: LAURA study design



*Patients with a positive local EGFR test result (cobas® v2 or FoundationOne® CDx test) did not require part I screening.
Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; CR, complete response; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; Ex19del, exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; NSCLC, non-small cell lung cancer; OS, overall survival; PFS2, time from randomisation to second progression or death on a subsequent treatment; PR, partial response; QD, every day; RECIST, Response Evaluation Criteria in Solid Tumours; SCRT, sequential chemoradiotherapy; SD, stable disease; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy or death; UICC, Union for International Cancer Control.
Source: CSR.[10]

Table 5: Summary of LAURA methodology

Trial number (acronym)	**LAURA**
Settings and locations	121 sites in 17 countries across Europe, Asia-Pacific, North America, and South America
Trial design	Ongoing, randomised, double-blind, placebo-controlled, multicentre, international study
Eligibility criteria for participants	Adult patients (aged ≥18, or aged ≥20 from Japan) with histologically confirmed primary NSCLC of predominantly non-squamous histology with locally advanced, unresectable disease. Patients must have World Health Organization (WHO) performance status 0–1
Sample size	A sample size of approximately 200 eligible patients was planned to provide sufficient (90%) power to demonstrate statistical significance in the primary endpoint Number of randomised patients: • Osimertinib, N=143 • Placebo, N=73
Planned analysis	For the planned analysis, the primary endpoint of PFS per BICR and the secondary endpoint of CNS PFS were tested at the primary analysis when 120 progression events have been observed in 200 patients (60% maturity). Analyses presented in this submission were based on the primary PFS analysis conducted at a data cut-off (DCO) date of 05 January 2024 The secondary endpoint of OS was tested at the primary analysis and will be tested at the final analysis. An interim analysis of OS (19.9% maturity of data) was conducted at the time of the primary analysis. The final analysis of OS will occur when approximately 120 death events have been reported in 200 patients (60% maturity)
Trial drugs	**Osimertinib arm (N=143)** Osimertinib 80 mg once daily (taken as a single oral dose ~24 hours apart, with ~240 ml of water, with or without food). The initial dose could be reduced to 40 mg once daily in the case of clinically significant AEs or unacceptable toxicity. Dose interruptions were also permitted for the same reasons Once the dose of osimertinib/placebo was reduced to 40 mg QD, the patient was to remain on the reduced dose until termination from study treatment. Re-challenge of osimertinib 80 mg/placebo was not allowed **Placebo arm (N=73)** Matching placebo. Patients in both treatment arms received randomised treatment until RECIST 1.1-defined disease progression, or unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met

	Patients assigned to osimertinib could continue receiving osimertinib (open-label) after BICR-confirmed progression if, in the opinion of their treating physician, they were continuing to derive clinical benefit. Patients assigned to placebo could switch to open-label osimertinib after BICR-confirmed progression, according to local clinical practice and the judgement of their treating physician. Open-label osimertinib treatment could continue until the patient stopped deriving clinical benefit as judged by the investigator, at which point open-label osimertinib was to be discontinued
Permitted and disallowed concomitant medication	**Permitted concomitant medications** Any medication to support safety and wellbeing of the patient may have been given according to local standards of care and at the discretion of the investigator **Disallowed concomitant medications** • Medications, herbal supplements and/or ingestion of foods that are known to be potent inducers of CYP3A4 (whenever feasible) • Other anti-cancer therapies, investigational agents and radiotherapy • Pre-medication including for the management of diarrhoea, nausea and vomiting was not allowed before the first dose of study drug • Medications that prolong the QT interval and are clearly associated with a known risk of Torsades de Pointes • Patients taking rosuvastatin had creatine phosphokinase levels monitored, with rosuvastatin use stopped upon patient experiences of AEs suggestive of muscle toxicity • Medications whose disposition is dependent on breast cancer resistance protein with a narrow therapeutic index were closely monitored in for signs of changed tolerability while receiving osimertinib
Method of randomisation and blinding	Patients were randomised in a 2:1 ratio to osimertinib using a central interactive voice/web response system. Randomisation was stratified by sequence of CRT (concurrent versus sequential), disease stage prior to CRT (IIIA versus IIIB/IIIC), and the Chinese cohort (patient enrolled at a Chinese site and declaring themselves of Chinese ethnicity versus enrolled at a non-Chinese site or patient declaring themselves of non-Chinese ethnicity). Randomisation occurred ≤ 6 weeks following completion of CRT
Primary outcome	PFS: time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression), by BICR assessment according to RECIST 1.1 A sensitivity analysis of investigator-assessed PFS according to RECIST v1.1 was also conducted
Other outcomes	**Key secondary endpoints:** • OS • CNS PFS **Other secondary endpoints:**

	• ORR • DoR • Depth of response • DCR • TTDM • TTD **Post-progression endpoints:** • PFS2 • TFST • TSST **Health-related quality of life outcomes:** • Time to symptom deterioration • Symptom improvement rate • Changes from baseline in each of the PRO symptom scores • The EQ-5D-5L health state utility index
Other outcomes used in the economic model/specified in the scope	• Time to treatment discontinuation
Pre-planned subgroups	Pre-specified subgroup analyses of PFS were conducted for age (< 65 versus ≥65), sex (male versus female), ethnicity (patients enrolled at a Chinese site and declaring themselves of Chinese ethnicity versus patients enrolled at non-Chinese site or patients declaring themselves of non-Chinese ethnicity), smoking history (current/former [yes] versus never [no]), prior CRT strategy (CCRT versus SCRT), disease stage prior to CRT (IIIA versus IIIB/IIIC), EGFR mutation type (Ex19del or L858R), race (Asian versus non-Asian) and response prior to CRT (CR vs PR vs SD vs NE)

Abbreviations: AE, adverse event; BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; CNS, central nervous system; CR, complete response; CRT, chemoradiation; CYP3A4, cytochrome P450 3A4; DCO, data cut-off; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; Ex19del, exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; PR, partial response; PRO, patient-reported outcome; QD, every day; RECIST, Response Evaluation Criteria in Solid Tumours; SCRT, subsequent chemoradiotherapy; SD, stable disease; 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; WHO, World Health Organization.
Source: CSR.[10]

Table 6: Eligibility criteria - LAURA

Inclusion	Exclusion
• Males and females aged ≥18 years of age (≥20 years in Japan) • Histologically confirmed NSCLC of predominantly non-squamous pathology with locally advanced, unresectable disease. The tumour harboured one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity (Ex19del or L858R), either alone or in combination with other EGFR mutations, assessed by cobas® EGFR Mutation Test v2 (Roche Diagnostics) or FoundationOne® test in a CLIA certified (USA sites) or an accredited local laboratory (sites outside of the USA) or by central testing (cobas® v2 only) • Patients must have received either concurrent chemoradiation or sequential chemoradiation including at least 2 cycles of platinum-based chemotherapy and a total dose of radiation of 60 Gy ±10% (54 to 66 Gy); chemoradiation had to be completed ≤6 weeks prior to randomisation • Patients must not have had disease progression during or following definitive platinum-based, chemoradiation therapy • WHO PS of 0 to 1 • Life expectancy >12 weeks at Day 1 • For patients of childbearing potential, the following stipulations apply: – Sexually active patients must use adequate contraceptive measures – May choose to practice complete abstinence, if consistent with the patient's preferred lifestyle, as an acceptable form of contraception – Must have a negative pregnancy test prior to the first dose of study drug – Must not be breastfeeding – Sexually active patients not using contraceptive measures must	• Patients with spinal cord compression; symptomatic and unstable brain metastases, except for those who had completed definitive therapy, were not on steroids, and had a stable neurological status for ≥2 weeks after completion of the definitive therapy and steroids • Mixed small cell and NSCLC histology • Past medical history of ILD prior to chemoradiation • Symptomatic pneumonitis following chemoradiation • Any unresolved toxicities from prior chemoradiation therapy greater than CTCAE Grade 2 • Any of the following cardiac criteria: – Mean resting QTc >470 msec, obtained from 3 ECGs – Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG – Any factors that increased the risk of QTc prolongation or risk of arrhythmic events • Inadequate bone marrow reserve or organ function • History of other malignancies (not including adequately treated non-melanoma skin cancer or lentigo maligna, curatively treated in-situ cancer, or other solid tumours curatively treated with no evidence of disease for >5 years following the end of treatment and which, in the opinion of the treating physician, do not have a substantial risk of recurrence of the prior malignancy) • Evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus • Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib • Prior treatment with any prior chemotherapy, radiation therapy, immunotherapy or investigational agents for NSCLC outside of that received in the definitive setting for Stage III disease • Prior treatment with an EGFR-TKI • Major surgery within 4 weeks of the first dose of the study drug • Use of medications or herbal supplements known to be strong inducers of CYP3A4 (at least 3 weeks prior) • Contraindication to MRI, including claustrophobia, pacemakers, metal implants, intracranial surgical clips and metal foreign bodies

Inclusion	Exclusion
provide evidence of non-childbearing potential	

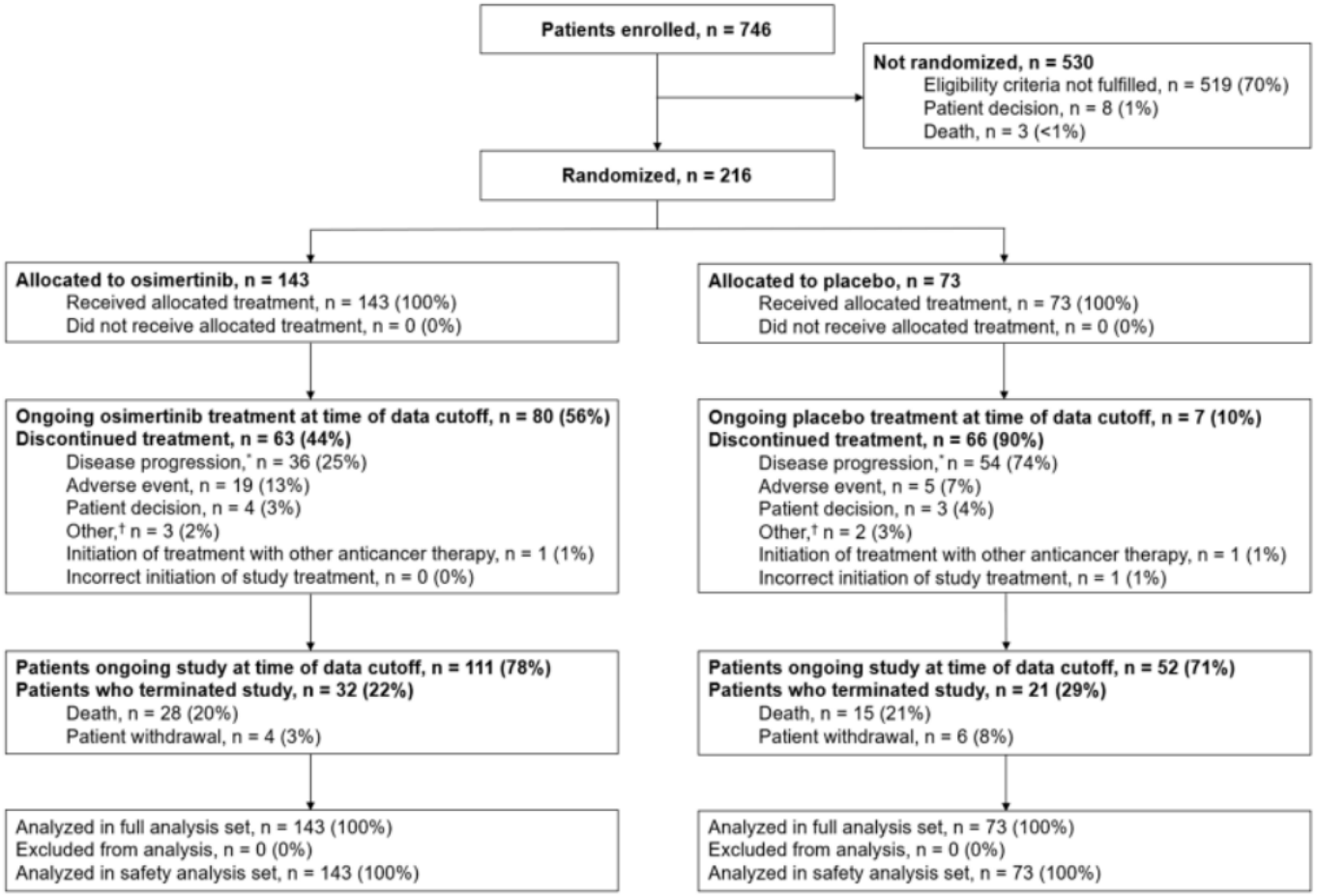
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; CYP3A4, cytochrome P450 3A4; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; ILD, interstitial lung disease; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PS, performance status; QTc, corrected QT interval; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.
Source: ClinicalTrials.gov (NCT03521154) and Lu et al., (2021).[68, 71]

B.2.3.2 Patient disposition

Patients were enrolled at 121 sites in 17 countries across Europe, Asia-Pacific, North America, and South America. In total, 216 patients were randomised (143 to osimertinib and 73 to placebo), with all randomised patients receiving at least one dose of study treatment (Figure 4).[10]

At the time of the primary DCO 40.3% of patients were ongoing with their randomised treatment (55.9% [80 patients] in the osimertinib arm and 9.6% [7 patients] in the placebo arm continuing to receive treatment). In total, 63 patients (44.1%) in the osimertinib arm and 66 patients (90.4%) in the placebo arm had discontinued study treatment. The most common reason for treatment discontinuation in both treatment arms was BICR-assessed disease progression (36 patients in the osimertinib arm and 54 patients in the placebo arm). At the primary DCO, the majority of patients remained in the study (111 patients in the osimertinib arm and 52 in the placebo arm), with the main reason for termination being death in both treatment arms (28 patients in the osimertinib arm and 15 patients in the placebo arm).

Figure 4: Patient disposition in LAURA



Abbreviations: BICR, blinded independent central review; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
*Assessed by blinded independent central review (per RECIST v1.1) prior to primary progression-free survival analysis. †Any reason not specifically recorded. ‡Percentages calculated using patients with BICR-assessed disease progression in each treatment group as denominator: osimertinib, n=53; placebo, n=62.
Source: Lu et al. (2024).[67]

B.2.3.3 Baseline characteristics and demographics

Overall, demographics and patient characteristics were generally well balanced between treatment arms. The majority of patients randomised in the study were female (61.1%), Asian (82.4%), never-smokers (69.9%), with a median age of 62.5 years (range: 36 to 84 years). In total, 31.9% of patients were aged between ≥ 65 and < 75 years, and 12.5% of patients were aged ≥ 75 years (Table 7).

Disease characteristics were also generally balanced between treatment arms, with the exception of WHO performance status (PS). Per protocol, all patients had a WHO PS of 0 (51.4%) or 1 (48.6%) at randomisation; however, a lower proportion of patients with a WHO PS of 1 were randomised to the osimertinib arm (44.1%) compared with the placebo arm (57.5%). This difference was not considered impactful on the evaluation of efficacy and safety in the individual treatment arms. A greater proportion of patients were randomised in the study with stage IIIB disease prior to CRT (48.6%) than those with both stage IIIA (35.2%) and stage IIIC (16.2%) disease, which was balanced between treatment arms (Table 8).

Table 7: Demographic characteristics of participants in LAURA across treatment groups (FAS)

LAURA Baseline characteristics	Osimertinib (N=143)	Placebo (N=73)	Total (N=216)
Age (years)			
Median (min, max)	62.0 (36, 84)	64.0 (37, 83)	62.5 (36, 84)
Age group (years), n (%)			
<50	24 (16.8)	12 (16.4)	36 (16.7)
≥50 to <65	57 (39.9)	27 (37.0)	84 (38.9)
≥65 to <75	49 (34.3)	20 (27.4)	69 (31.9)
≥75	13 (9.1)	14 (19.2)	27 (12.5)
Sex, n (%)			
Female	90 (62.9)	42 (57.5)	132 (61.1)
Race, n (%)			
Asian	116 (81.1)	62 (84.9)	178 (82.4)
White	20 (14.0)	10 (13.7)	30 (13.9)
American Indian or Alaskan Native	2 (1.4)	1 (1.4)	3 (1.4)
Other	5 (3.5)	0	5 (2.3)
Smoking status, n (%)			
Never	102 (71.3)	49 (67.1)	151 (69.9)
Smoker - Current	4 (2.8)	1 (1.4)	5 (2.3)
Smoker - Former	37 (25.9)	23 (31.5)	60 (27.8)

Abbreviations: FAS, full analysis set.
Source: CSR.[71]

Table 8: Disease characteristics at baseline (FAS)

LAURA Baseline characteristics	Osimertinib (N=143)	Placebo (N=73)	Total (N=216)
WHO PS, n (%)			
0 (Normal activity)	80 (55.9)	31 (42.5)	111 (51.4)
1 (Restricted activity)	63 (44.1)	42 (57.5)	105 (48.6)
AJCC stage (8th edition) at initial diagnosis, n (%)†			
Stage IIIA	52 (36.4)	24 (32.9)	76 (35.2)
Stage IIIB	67 (46.9)	38 (52.1)	105 (48.6)
Stage IIIC	24 (16.8)	11 (15.1)	35 (16.2)

LAURA Baseline characteristics	Osimertinib (N=143)	Placebo (N=73)	Total (N=216)
Histology type, n (%)			
Adenocarcinoma	139 (97.2)	69 (94.5)	208 (96.3)
Squamous cell carcinoma	3 (2.1)	2 (2.7)	5 (2.3)
Other‡	1 (0.7)	2 (2.7)	3 (1.4)
Time from unresectable Stage III diagnosis to randomisation (days)			
Mean (StD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]
Prior CRT strategy, n (%)			
CCRT	131 (91.6)	62 (84.9)	193 (89.4)
SCRT	12 (8.4)	11 (15.1)	23 (10.6)
Response to prior CRT, n (%)			
CR	4 (2.8)	3 (4.1)	7 (3.2)
PR	67 (46.9)	27 (37.0)	94 (43.5)
SD	61 (42.7)	37 (50.7)	98 (45.4)
PD	0	0	0
Non-evaluable	11 (7.7)	6 (8.2)	17 (7.9)
Overall extent of disease at study entry, n (%)			
Metastatic§	[redacted]	[redacted]	[redacted]
Locally advanced¶	[redacted]	[redacted]	[redacted]
Missing††	[redacted]	[redacted]	[redacted]
Tissue EGFRm status at screening, n (%)			
Ex19del positive	74 (51.7)	43 (58.9)	117 (54.2)
L858R positive	68 (47.6)	30 (41.1)	98 (45.4)
Missing¶¶	[redacted]	[redacted]	[redacted]

† Disease stage summarised based on values entered into the eCRF and categorised prior to CRT according to AJCC/UICC 8th Edition. ‡ Per the eCRF, these patients had adenosquamous histology and were eligible for inclusion. § Patient has any metastatic site of disease. ¶ Patient has only locally advanced sites of disease. †† These patients had a complete response to prior CRT and therefore their disease was not detectable at randomisation for classification. ‡‡ Summarised based on central cobas® EGFR plasma testing results. §§ Status was unknown due to the unavailability or inadequacy of plasma samples for central testing. ¶¶ Patients randomised without an approved local positive EGFR test result or central EGFR test result.
Abbreviations: AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; CR, complete response; CRT, chemoradiotherapy; ctDNA, circulating tumour DNA; eCRF, electronic case report form; EGFRm, epidermal growth factor receptor mutation positive; Ex19del, exon 19 deletion, an in-frame deletion occurring within exon 19, which encodes part of the kinase domain; FAS, full analysis set; L858R, sensitising mutation in the EGFR gene with substitution of a leucine with an arginine at position 858 in exon 21; PD, progressed disease; PR, partial response; PS, performance status; SCRT, subsequent chemoradiotherapy; SD, stable disease; StD, standard deviation; WHO, World Health Organization.
Source: CSR.[71]

B.2.3.3.1 Prior anti-cancer therapies

All patients received both platinum-based chemotherapy and radiotherapy prior to randomisation. A summary of prior CRT received by patients in the LAURA trial is presented in Table 9.

Table 9: Summary of prior anti-cancer therapies received by patients in LAURA (FAS)

Type of prior chemoradiotherapy, n (%)	Osimertinib (N=143)	Placebo (N=73)
Chemotherapy	143 (100)	73 (100)
Platinum-based agent	143 (100)	73 (100)
Carboplatin	75 (52)	44 (60)
Cisplatin	66 (46)	29 (40)
Nedaplatin	2 (1)	0
Non-platinum-based agent	143 (100)	73 (100)
Docetaxel	3 (2)	5 (7)
Etoposide	15 (10)	8 (11)
Gemcitabine	1 (1)	1 (1)
Paclitaxel	69 (48)	34 (47)
Pemetrexed	39 (27)	22 (30)
Vinorelbine	18 (13)	7 (10)
Radiotherapy	143 (100)	73 (100)
3D Conformal	44 (31)	18 (25)
IMRT	99 (69)	55 (75)

Abbreviations: IMRT, intensity-modulated radiation therapy; FAS, full analysis set.
Source: Lu et al. (2024).[67]

B.2.3.3.2 Determination of EGFRm status

The prevalence of confirmed EGFRm status was broadly balanced between treatment arms, as confirmed by either a prospective central or pre-existing local EGFRm test. Overall, 117 patients (54.2%) had Ex19del mutations, and 98 patients (45.4%) had L858R mutations (Table 8).

B.2.3.3.3 Use of concomitant medications

The majority of patients ([redacted] patients [[redacted]%]) received at least one permitted concomitant medication during the study. The most commonly used concomitant

medications (reported for ≥20% of patients in either treatment arm) are summarised in Table 10.

Table 10: Concomitant medications (≥20% of patients in either treatment arm) (FAS)

ATC Classification Generic term	Number (%) of patients		
	Osimertinib (N=143)	Placebo (N=73)	Total (N=216)
Number of patients with a concomitant medication	[redacted]	[redacted]	[redacted]
Glucocorticoids	[redacted]	[redacted]	[redacted]
Proton pump inhibitors	[redacted]	[redacted]	[redacted]
Mucolytics	[redacted]	[redacted]	[redacted]
Anilides	[redacted]	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]	[redacted]
Opium alkaloids and derivatives	[redacted]	[redacted]	[redacted]
COVID-19 vaccines	[redacted]	[redacted]	[redacted]
Combinations of penicillins (incl. beta-lactamase inhibitors)	[redacted]	[redacted]	[redacted]
Opium derivatives and expectorants	[redacted]	[redacted]	[redacted]
HMG COA reductase inhibitors	[redacted]	[redacted]	[redacted]
Benzodiazepine derivatives	[redacted]	[redacted]	[redacted]

A patient can have one or more generic terms reported under a given ATC text. Includes medications which are ongoing or with a stop date on or after the first dose date of study treatment (and which started prior to or during study treatment).
Abbreviations: ATC, Anatomical Therapeutic Chemical; HMG, β-Hydroxy β-methylglutaryl; COA, coenzyme A; FAS, full analysis set.
Source: CSR.[71]

B.2.3.3.4 Post-study anti-cancer therapies

At the 05 January 2024 DCO, 80 patients (55.9%) in the osimertinib arm continued to receive randomised study treatment, in comparison with 7 patients (9.6%) in the placebo arm (Table 11). Of the 63 patients in the osimertinib arm who had discontinued study treatment, 42 patients (66.7%) received a subsequent post-treatment disease-related anti-cancer therapy. In the placebo arm, of the 66 patients who had discontinued study treatment, 57 patients (86.4%) received a subsequent post-treatment disease-related anticancer therapy. The majority of patients in both treatment arms received

[redacted]

[redacted]. Post-study anti-cancer treatments in the osimertinib arm varied, with the most common post-treatment anti-cancer therapies being EGFR-TKIs, cytotoxic chemotherapy and radiotherapy. The most common post-treatment anti-cancer therapy in the placebo treatment arm was overwhelmingly an EGFR-TKI, with (57/66 patients [86.4%]) receiving these compounds. Moreover, [redacted]% of patients in the placebo arm received osimertinib as their first disease-related anticancer treatment after study treatment discontinuation ([redacted] patients).

Table 11: Post study treatment anticancer therapy (FAS)

	Number (%) patients†	
	Osimertinib (N=143)	**Placebo (N=73)**
Discontinued randomised study treatment	63 (44.1)	66 (90.4)
Any post-treatment anti-cancer therapy	42 (29.4)	57 (78.1)
Received 1 line of therapy	[redacted]	[redacted]
Received 2 lines of therapy	[redacted]	[redacted]
Received 3 lines of therapy	[redacted]	[redacted]
Received 4 lines of therapy	[redacted]	[redacted]
Received ≥5 lines of therapy	[redacted]	[redacted]
No post-treatment anti-cancer therapy	[redacted]	[redacted]
Ongoing randomised study treatment	21 (14.7)	9 (12.3)
Types of post-treatment anticancer therapy received		
EGFR-TKI	28 (19.6) [44.4]	57 (78.1) [86.4]
First or second-generation EGFR-TKI	12 (8.4) [19.0]	7 (9.6) [10.6]
Third generation EGFR-TKI	16 (11.2) [25.4]	52 (71.2) [78.8]
Osimertinib	15 (10.5) [23.8]	51 (69.9) [77.3]
Aumolertinib	1 (0.7) [1.6]	1 (1.4) [1.5]
Furmonertinib	0	1 (1.4) [1.5]
Cytotoxic chemotherapy	21 (14.7) [33.3]	11 (15.1) [16.7]
Platinum compounds	19 (13.3) [30.2]	7 (9.6) [10.6]
Folic acid analogues (pemetrexed)	[redacted]	[redacted]
Taxanes	[redacted]	[redacted]
Other chemotherapy‡	[redacted]	[redacted]
Radiotherapy	21 (14.7) [33.3]	5 (6.8) [7.6]
VEGF Inhibitor – Monoclonal antibody	8 (5.6) [12.7]	5 (6.8) [7.6]
PD-1/PD-L1 inhibitor – Immunotherapy	5 (3.5) [7.9]	1 (1.4) [1.5]

	Number (%) patients†	
	Osimertinib (N=143)	Placebo (N=73)
Other	2 (1.4) [3.2]	2 (2.7) [3.0]

†The number of patients is shown with percentages (%) calculated as the proportion of patients in the FAS and secondly [%] as the proportion of patients who discontinued randomised study treatment. ‡Includes pyrimidine analogues, vinca alkaloids and analogues, podophyllotoxin derivatives, and topoisomerase 1 inhibitors.
A patient may be counted in multiple rows if they receive more than one post-treatment anticancer therapy. Includes anticancer therapies with a start date after the last dose date of study treatment.
Abbreviations: EGFR, epidermal growth factor receptor; FAS, full analysis set; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
Source: CSR.[71]

B.2.3.4 Expert elicitation/opinion

An advisory board was conducted in September 2024 with 8 oncologists (5 clinical oncologists and 3 medical oncologists) based in the UK.[15] The format of the advisory board consisted of an online forum where clinicians were able to respond to questions in real time. The objective of the advisory board was:

- To discuss the current clinical pathway for patients with locally advanced, unresectable EGFRm NSCLC
- To understand clinician views on the data from the LAURA study and the potential impact to UK practice

Insights from the advisory board are provided throughout the dossier. Summary of the discussion is provided as data on file (AstraZeneca UK Data on file. REF-258919. LAURA UK Advisory Boards: Results. January 2025).[15]

In addition, five one-to-one interviews were conducted with UK clinical experts with experience in treating NSCLC during November 2024. The interviews were used to inform clinical and resource use assumptions used in the economic model. The report is provided as data on file (AstraZeneca UK Data on file. REF-258919. LAURA UK Advisory Boards: Results. January 2025).[15]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Populations analysed

Details of the population analysis sets defined in LAURA along with their use in the study are presented in Table 12.

Table 12: Population analysis sets –LAURA

Analysis set (based on the global cohort)	Definition	Purpose
FAS	All randomised patients (as randomised, regardless of actual treatment; i.e. the ITT population). The FAS was used for all efficacy analyses, and treatment arms were compared on the basis of randomised study treatment.	Demography and baseline characteristics, efficacy analyses. HRQoL
EFR Analysis Set	A subset of patients of the FAS analysis set who had measurable disease at baseline according to the BICR of baseline imaging data.	Efficacy analyses
Safety Analysis Set	All randomised patients who received at least one dose of study treatment. Safety data were not formally analysed but are summarised descriptively according to treatment actually received (e.g., those randomised to treatment A but actually given treatment B) are summarised according to the treatment actually received in the relevant treatment arm).	Safety analyses

Abbreviations: BICR, blinded independent central review; FAS, full analysis set; EFR, evaluable for response; ITT, intention-to-treat; PK, pharmacokinetic.
Source: CSR.[71]

B.2.4.2 Hypothesis objective

The objective of LAURA was to demonstrate that osimertinib therapy could improve outcomes for patients with locally advanced EGFRm NSCLC compared with placebo. The hypothesis of improved PFS could be tested when 120 PFS events (approximately 60% data maturity) had occurred.

B.2.4.3 Statistical analysis

To ensure strong control of the type I error rate, α=0.05 (2-sided), the primary endpoint PFS and the key secondary endpoints OS and CNS PFS were tested in sequential order. The hierarchical testing procedure determined that if PFS was

statistically significant at the time of the primary PFS analysis, then subsequent hypothesis testing for OS and then to the CNS PFS would be performed at overall α=0.05 significance level (2-sided) using the Lan-DeMets spending function that approximates an O'Brien-Fleming approach. If any previous analysis in the sequence was not statistically significant, the alpha could not be transferred to subsequent analyses.

Statistical analyses were conducted for each endpoint as follows:

- **PFS:** analysed using a log-rank test stratified by prior CRT, disease stage prior to CRT, and China cohort.
- **OS:** two analyses of OS were planned as part of the hierarchical testing procedure, the first was conducted at the time of the primary analysis of PFS, and a final analysis was planned to be performed at approximately 60% data maturity, when approximately 120 death events (across both arms) have occurred. OS data were analysed using the same methodology and model as for PFS analysis.
- **CNS PFS:** CNS PFS data were analysed using the same methodology and model as for PFS analysis, provided sufficient events were available for a meaningful analysis (≥ 20 CNS PFS events across both treatment arms with at least 5 events per arm).

B.2.4.4 Sample size and power calculation

Approximately 200 patients were required to be randomised in a 2:1 ratio (osimertinib to placebo). The primary endpoint was PFS assessed by BICR according to RECIST 1.1 in the full analysis set (FAS). The primary endpoint, BICR PFS, was analysed when approximately 120 PFS events had occurred (approximately 60% maturity). If the true PFS HR for the comparison of the two treatment arms was 0.53, 120 progression events would provide 90% power to demonstrate a statistically significant difference in PFS at a 5% two-sided significance level. This translates to an approximate improvement in median PFS from [redacted] months to [redacted] months with osimertinib treatment versus placebo. The minimum

critical HR is [redacted], which translates to an approximate median PFS [redacted]-month improvement, from [redacted] months to [redacted] months.

B.2.4.5 Data management and patient withdrawals

Patients were free to discontinue study treatment at any time without prejudice to further treatment. Patients were asked about the reason(s) for discontinuation of treatment and the presence of any AEs. A patient was still considered to be ongoing in the study if they did not withdraw their consent for the study and study visits continued according to the study plan. Patients may have been discontinued from all study treatments for the following reasons: Response Evaluation Criteria in Solid Tumors (RECIST) 1.1-defined progression (if the patient was no longer receiving clinical benefit), patient decision, AEs, severe non-compliance, incorrect initiation of study treatment, initiation of alternative anticancer therapy, or pregnancy. Upon discontinuation of all study treatments, patients were to be treated in accordance with the local standard of care.

The investigator informed patients who had decided to withdraw about modified follow-up option such as, telephone contact, a contact with a relative or treating physician, or information from medical records. If the patient withdrew consent for disclosure of future information, the sponsor could retain and continue to use any data collected before withdrawal of consent.

Any patient who failed to return for scheduled study visits or became unreachable were considered lost to follow-up with unknown vital status and therefore censored at the latest follow-up contact.

B.2.4.6 Participant flow in the relevant randomised controlled trials

From August 2018 to July 2022, 746 patients were enrolled in the study and underwent screening. Following confirmation of eligibility, a total of 216 patients at 121 study centres across 17 countries worldwide were randomly assigned to treatment. All 216 randomised patients received at least one dose of study treatment. A total of 143 patients were assigned to osimertinib arm and 73 patients received placebo. At the DCO date, 80 patients (55.9%) in the osimertinib arm and 7

patients (9.6%) in the placebo arm were receiving ongoing treatment. See Appendix D for full details of participant flow.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for LAURA is provided in Table 13.

Table 13: Quality assessment results for LAURA

Trial number (acronym)	yes/no/not clear/NA
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Abbreviations: NA, not applicable.

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 LAURA

Results presented in this submission were based on the primary PFS analysis conducted at a DCO date of 05 January 2024. An interim analysis of OS (19.9% maturity of data) was conducted at the time of the primary analysis.

B.2.6.1.1 Primary efficacy outcome

B.2.6.1.1.1 Progression-free survival (05 January 2024 DCO)

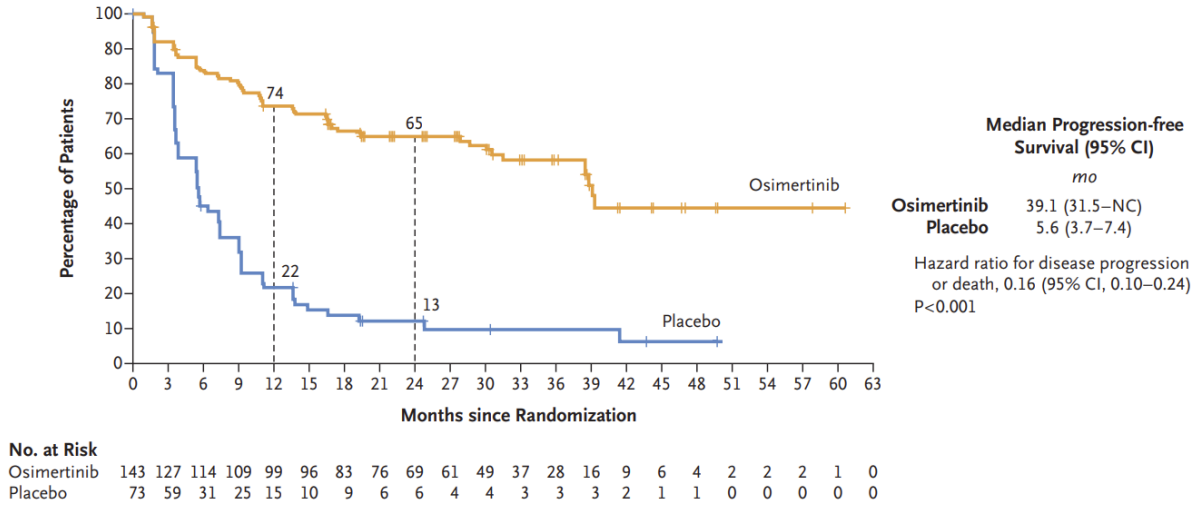
Delaying disease progression is a key treatment goal for patients with unresectable locally advanced EGFRm NSCLC because patients who progress to metastatic

disease have lower survival rates, a high disease burden associated with a lower quality of life, and have a higher economic impact on the health system.[72]

In LAURA, PFS was defined as the length of time from randomisation until the date of objective disease progression or death. Progression-free survival was considered the most appropriate endpoint for LAURA and is a well-established clinical outcome in oncology that is not affected by crossover or confounding due to later lines of therapy. Progression was defined according to RECIST 1.1, which is the well-recognised international standard for measurement of tumour burden.[73]

At the primary PFS per BICR analysis, osimertinib reduced the risk of disease progression or death by 84% compared with placebo (HR: 0.16 [95% CI: 0.10, 0.24]; p<0.001), with an unprecedented clinically meaningful and statistically significant improvement in median PFS of 33.6 months (Figure 5). In total, there were 57 PFS events (39.9%) in the osimertinib arm and 63 PFS events (86.3%) in the placebo arm, with an overall data maturity of 55.6% (Table 14). An early and sustained separation in the KM curves in favour of the osimertinib arm was observed from the first RECIST 1.1 scan at 8 weeks post-randomisation and was sustained over the follow-up period (Figure 5).

Figure 5: KM plot of progression-free survival (months) by BICR (FAS)



Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival.
DCO: 05 January 2024
Source: Lu et al. (2024).[67]

Table 14: Progression-free survival by BICR (FAS)

	Osimertinib (N=143)	Placebo (N=73)
Progression status, n (%)		
Progression - total†	**57 (39.9)**	**63 (86.3)**
RECIST progression	[redacted]	[redacted]
Target lesions‡	[redacted]	[redacted]
Non-target lesions‡	[redacted]	[redacted]
New lesions‡	[redacted]	[redacted]
Death in the absence of progression	[redacted]	[redacted]
Censored patients, n (%)	[redacted]	[redacted]
Censored RECIST progression §	[redacted]	[redacted]
Censored death§	[redacted]	[redacted]
Progression free at time of analysis	[redacted]	[redacted]
Withdrawn consent	[redacted]	[redacted]
Comparison between groups		
Hazard ratio (95% CI) ¶	0.16 (0.10, 0.24)	
2-sided p-value¶	<0.0001	
Median PFS		
Median PFS (months) (95% CI)††	39.13 (31.51, NC)	5.55 (3.71, 7.43)
PFS rate at 6 months (%) (95% CI)††	[redacted]	[redacted]
PFS rate at 12 months (%) (95% CI)††	73.7 (65.4, 80.3)	21.8 (13.0, 32.1)

	Osimertinib (N=143)	Placebo (N=73)
PFS rate at 18 months (%) (95% CI)††	[redacted]	[redacted]
PFS rate at 24 months (%) (95% CI)††	65.1 (56.4, 72.6)	12.5 (5.9, 21.6)
PFS rate at 36 months (%) (95% CI)††	[redacted]	[redacted]
Median (range) duration of follow-up in all patients (months)	[redacted]	[redacted]
Median (range) duration of follow-up in censored patients (months)	[redacted]	[redacted]

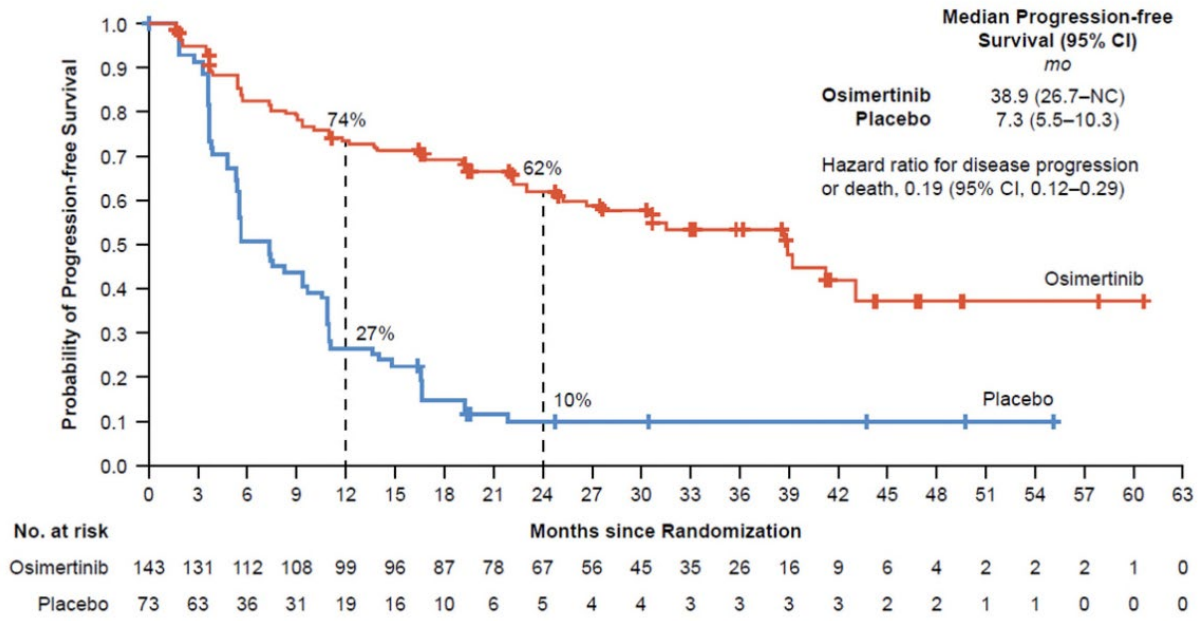
†PFS events that did not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) were censored; ‡Target lesions, non-target lesions, and new lesions are not necessarily mutually exclusive categories; §Occurred after 2 or more consecutive missed visits following last non-missing RECIST assessment (or randomisation); ¶The analysis was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there were < 10 events per stratum. A HR <1 favours osimertinib to be associated with a longer PFS than placebo; †† Calculated using the KM technique.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; HR, hazard ratio; IxRS, interactive voice or web response system; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SAP, Statistical Analysis Plan.
DCO: 05 January 2024
Source: CSR and Lu et al 2024.[10, 67]

B.2.6.1.1.2 Sensitivity analysis of the primary outcome (05 January 2024 DCO)

Ascertainment bias was assessed by analysis of PFS by investigator assessment according to RECIST 1.1 in the FAS. A consistent and significant PFS gain was observed following treatment with osimertinib in the investigator assessed analysis and was consistent with the BICR-based analysis. At the 05 January 2024 DCO, 125 PFS had occurred, comprising of 62 PFS events (43.4%) in the osimertinib arm and 63 PFS events (86.3%) in the placebo arm, with overall data maturity of [redacted]%.

Consistent with the BICR-based analysis, the HR was 0.19 (95% CI: 0.12, 0.29; nominal p<0.001). An approximate 31.6-month reduction in the risk of disease progression or death was observed in the osimertinib arm compared with the placebo arm (Figure 6).

Figure 6: KM plot of progression-free survival (months) by investigator assessment (FAS)



Abbreviations: CI, confidence interval; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival.
DCO: 05 January 2024
Source: Lu et al. 2024.[67]

The KM curve of PFS by investigator assessment also demonstrated early separation between treatment arms in favour of osimertinib from the first RECIST 1.1 scan post-randomisation and throughout the remaining duration of follow-up (Figure 6).

Concordance between BICR and investigator assessment of PFS was high, with an [redacted]% agreement in the osimertinib arm, and a [redacted]% agreement in the placebo arm.

B.2.6.1.2 Secondary efficacy outcomes

B.2.6.1.2.1 Central nervous system progression-free survival (DCO 05 January 2024)

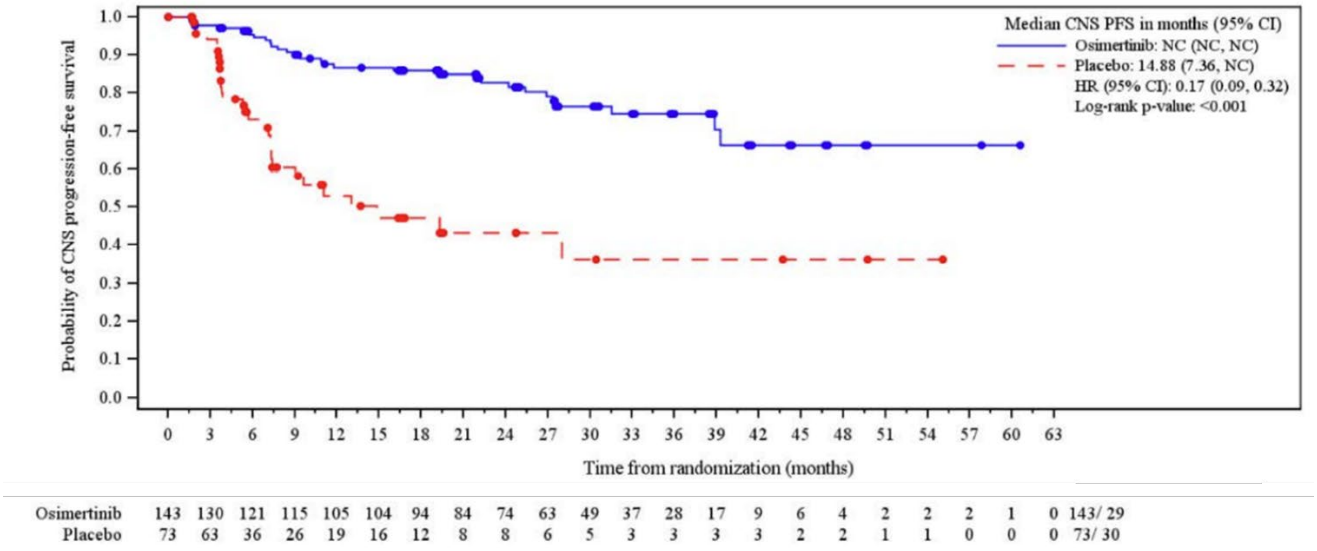
Central nervous system progression-free survival was defined as the time from randomisation until the date of CNS objective disease progression or death and was measured by neuroradiologist BICR. Patients with EGFRm NSCLC are at nearly double the risk of developing CNS metastases compared with patients with wtEGFR NSCLC (38% vs 70%), which are associated with limited life expectancy, a decline in

neurological and cognitive functions, complex symptoms, and a rapid deterioration in QoL.[8, 52, 53]

Osimertinib treatment demonstrated a nominally statistically significant and clinically meaningful 83% reduction in the risk of CNS progression or death by neuroradiologist BICR compared with placebo (HR: 0.17 [95% CI: 0.09, 0.32], nominal p<0.001), with an overall data maturity of 27.3% (Table 15).

The KM curve of CNS PFS by neuroradiologist BICR demonstrated early separation between treatment arms in favour of osimertinib from the first post-baseline scan at week 8, with the separation of curves sustained throughout the follow-up period (Figure 7). A sensitivity analysis of CNS PFS by investigator assessment demonstrated a HR of 0.19 (95% CI: 0.10, 0.36) which was consistent with the analysis of CNS PFS by BICR. Moreover, the cumulative incidence rate of CNS progression at 12 months was four times lower in the osimertinib arm (9% [95% CI: 5, 14]) compared with the placebo arm (36% [95% CI: 24, 47]) (Figure 8).

Figure 7: KM plot of central nervous system progression-free survival by neuroradiologist BICR assessment (DCO 05 January 2024) (FAS)



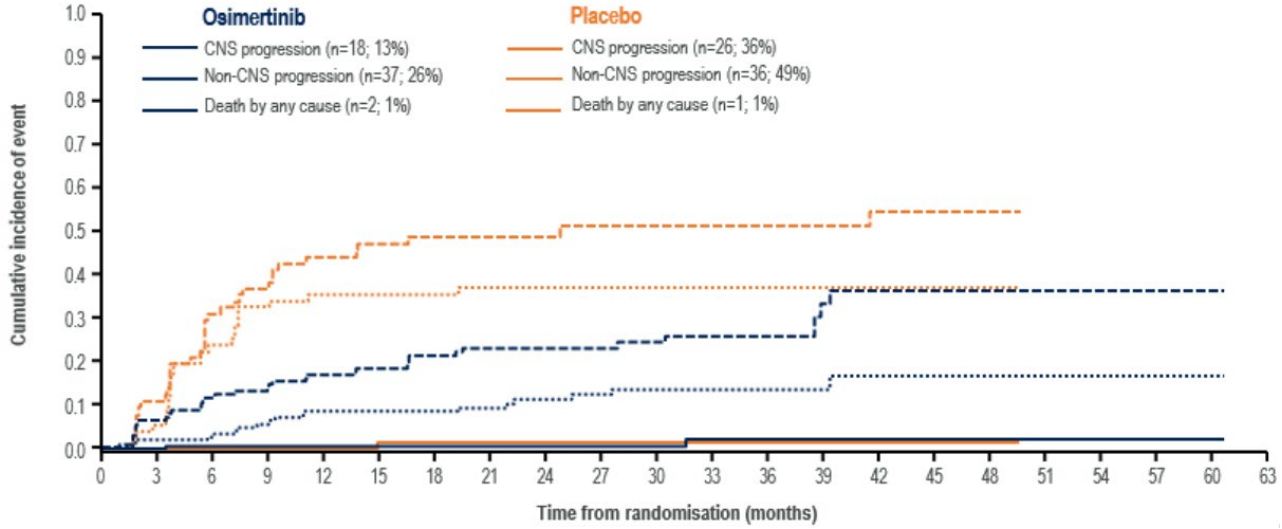
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival.
Source: Lu et al. (2024).[70]

Table 15: Central nervous system progression-free survival by neuroradiologist BICR (DCO 05 January 2024) (FAS)

	Osimertinib (N=143)	Placebo (N=73)
Progression status, n (%)		
Progression - total†	**29 (20.3)**	**30 (41.1)**
CNS RECIST progression	18 (12.6)	26 (35.6)
Target lesions‡§	[redacted]	[redacted]
Non-target lesions‡§	[redacted]	[redacted]
New lesions‡	[redacted]	[redacted]
Death in the absence of progression	11 (7.7)	4 (5.5)
Censored patients	114 (79.7)	43 (58.9)
Censored CNS RECIST progression¶	[redacted]	[redacted]
Censored death¶	[redacted]	[redacted]
No CNS event observed	[redacted]	[redacted]
CNS progression free at time of analysis	[redacted]	[redacted]
Non-CNS progression observed	[redacted]	[redacted]
Withdrawn consent	[redacted]	[redacted]
Comparison between groups		
Hazard ratio (95% CI)††	0.17 (0.09, 0.32)	
2-sided p-value††	<0.001	
Median CNS PFS		
Median CNS PFS (months) (95% CI)‡‡	NC (NC, NC)	14.88 (7.36, NC)
CNS PFS rate at 12 months (%) (95% CI)‡‡	[redacted]	[redacted]
CNS PFS rate at 24 months (%) (95% CI)‡‡	[redacted]	[redacted]
Median (range) follow-up for CNS PFS in all patients (months)	[redacted]	[redacted]
Median (range) follow-up for CNS PFS in censored patients (months)	[redacted]	[redacted]

†CNS PFS events that did not occur within 2 scheduled visits (plus visit window) of the last non-missing assessment (or randomisation) are censored; ‡Target lesions, non-target lesions and new lesions are not mutually exclusive categories; §It is noted that whilst patients were free of CNS disease at baseline according to the Investigator, the neuroradiologist BICR reader could independently assign target and non-target lesions during CNS BICR assessment; ¶Occurred after 2 or more consecutive missed visits following last non-missing RECIST assessment (or randomisation); ††The analysis was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there are < 10 events per stratum. A HR <1 favours osimertinib to be associated with a longer CNS PFS than placebo; ‡‡Calculated using the KM technique.
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; HR, hazard ration; IxRS, interactive voice or web response system; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAP, Statistical Analysis Plan.
Source: CSR[10] and Lu et al. (2024).[70].

Figure 8: Cumulative incidence of CNS/non-CNS progression or death, competing risk analysis (FAS) (DCO 05 January 2024)



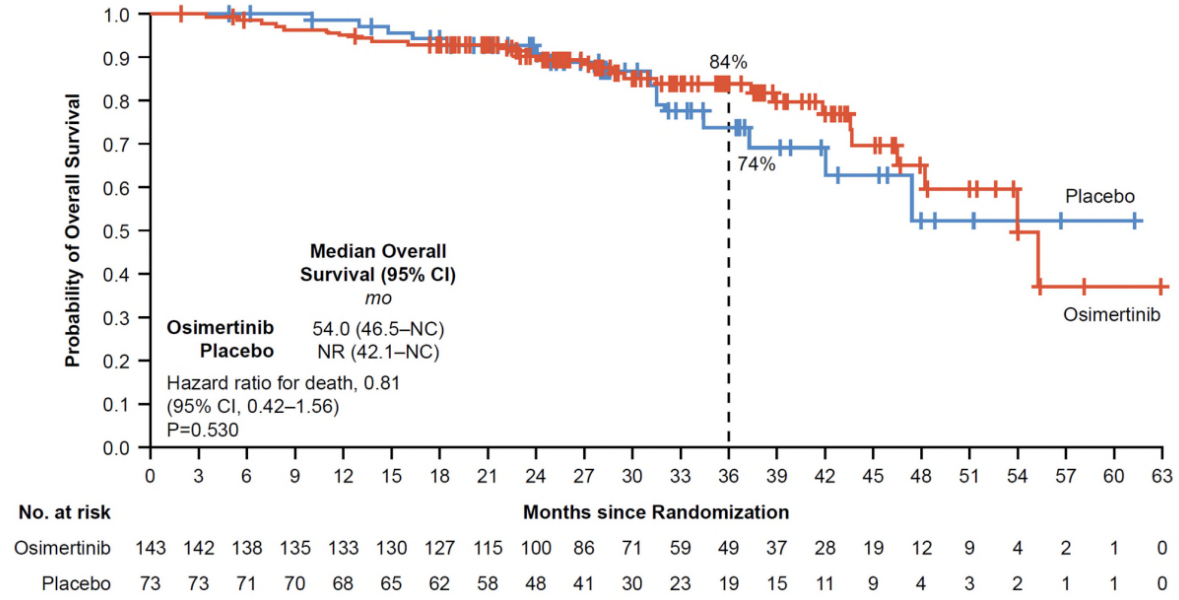
Analysis combines data from CNS BICR and Study BICR. Progression in the CNS includes patients who had documented radiological progression in the CNS at the same overall visit. Event time is the first occurrence of the event. The cumulative incidence function is calculated using the KM method.
Abbreviations: CNS, central nervous system; DCO, data cut-off, FAS, full analysis set.
Source: Lu et al. (2024).[70]

B.2.6.1.2.2 Overall survival

Overall survival was defined as the time from the date of randomisation until death due to any cause. Overall survival is a key outcome in oncology studies, however in patients with locally advanced, unresectable NSCLC, OS maturity can take a long time to achieve, and patients have a poor prognosis. Moreover, OS can be confounded by subsequent treatments and may not directly reflect the impact of the treatment effect under consideration.

An initial positive trend in OS was observed following treatment with osimertinib compared with placebo (Figure 9). At the interim OS analysis (05 January 2024) OS data were immature (19.9%), with 43 deaths across the 216 randomised patients (Table 16). There was a favourable trend towards improved OS with osimertinib versus placebo (HR: 0.81 [95% CI: 0.42, 1.56]; p=0.530) (Figure 9).

Figure 9: Kaplan-Meier plot of OS (months) (DCO 05 January 2024) (FAS)



Abbreviations: CI, confidence interval; DCO, data cut-off; FAS, full analysis set; NC, not calculable; NR, not recorded; OS, overall survival.
Source: Lu et al. (2024).[67]

Median OS in the osimertinib arm was 53.95 months (95% CI: 46.49, NC) and was not reached in the placebo arm (Table 16). It should be noted that the median OS for osimertinib was estimated based on a single event with few patients at risk and therefore, should be interpreted with caution.

Per protocol, all patients were offered open-label osimertinib following BICR-confirmed disease progression. Due to the high proportion of patients in the placebo arm who received osimertinib treatment after BICR-confirmed disease progression (50/62 patients [80.6%]), the OS results at the current DCO date should be interpreted in the context of the substantial degree of crossover.

Table 16: Overall survival (05 January 2024 DCO) (FAS)

	Osimertinib (N=143)	Placebo (N=73)
Survival status, n (%)		
Death	[redacted]	[redacted]
Censored patients	[redacted]	[redacted]
Still in survival follow-up†	[redacted]	[redacted]
Terminated Prior to death‡	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]
Comparison between groups		
Hazard ratio (95% CI)§	0.81 (0.42, 1.56)	
Adjusted 99.96% CI¶	0.25, 2.67	
2-sided p-value§	0.530	
Median overall survival		
Median OS (months) (95% CI)††	53.95 (46.49, NC)	NC (42.05, NC)
OS at 12 months (%) (95% CI)††	[redacted]	[redacted]
OS at 24 months (%) (95% CI)††	[redacted]	[redacted]
OS at 36 months (%) (95% CI)††	[redacted]	[redacted]
OS at 48 months (%) (95% CI)††	[redacted]	[redacted]
Median (range) follow-up for OS in all patients (months)	[redacted]	[redacted]
Median (range) follow-up for OS in censored patients (months)	[redacted]	[redacted]

†Includes patients known to be alive at DCO; ‡Includes patients with unknown survival status or patients who were lost to follow-up; §The analysis was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS, after applying the SAP rule to collapse strata if there were <10 events per stratum, provided there are more than 20 deaths across both treatment arms and at least 5 events per arm; ¶ Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary with the observed number of events, the boundary for declaring statistical significance is 0.00036 for a 5% overall alpha; ††Calculated using the KM technique.
Abbreviations: CI, confidence interval; CSR DCO, data cut-off; FAS, full analysis set; IxRS, interactive voice or web response system; KM, Kaplan-Meier; OS, overall survival; SAP, Statistical Analysis Plan.
Source: Lu et al. (2024);[67] CSR.[10]

B.2.6.1.2.3 Objective response rate (DCO 05 January 2024)

Objective response rate (ORR) was defined as the percentage of patients with at least one investigator-assessed visit response of complete response (CR) or partial response (PR), and is an important surrogate endpoint in oncology clinical trials which measures tumour shrinkage.[74]

Higher response rates were observed in the osimertinib arm compared with the placebo arm ([redacted]% versus [redacted]%, respectively), with an odds ratio of 2.77 (95% CI: 1.54, 5.08; nominal p<0.001) in favour of the osimertinib arm (Table 17). The majority of patients in the osimertinib arm had a best objective response of PR ([redacted]patients [[redacted]%]); in the placebo arm, most patients had a best objective response of stable disease (SD) ([redacted] patients [[redacted]%]).

Analysis of the confirmed responses only (responses confirmed at least 4 weeks after the initial response), were consistent and revealed a higher ORR in the osimertinib arm compared with placebo (53.8% versus 26.0%, respectively) (Table 17).

Table 17: Objective response by BICR (DCO 05 January 2024) (FAS)

	Osimertinib (N=143)	**Placebo (N=73)**
Analysis of ORR†		
Best objective response, n (%) [95% CI]‡		
Response	82 (57.3) [48.8, 65.6]	24 (32.9) [22.3, 44.9]
Complete response	3 (2.1)	1 (1.4)
Partial response	79 (55.2)	23 (31.5)
Non-response	[redacted]	[redacted]
Stable disease (≥8 weeks)	45 (31.5)	34 (46.6)
Progression	11 (7.7)	12 (16.4)
Not evaluable	5 (3.5)	3 (4.1)
Comparison between groups		
Odds ratio (95% CI)§	2.77 (1.54, 5.08)	
2-sided p-value¶	[redacted]	
Analysis of ORR – confirmed responses‡‡		
Best objective response, n (%) [95% CI] ‡		
Response	[redacted]	[redacted]
Complete response	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Non-response	[redacted]	[redacted]
Stable disease (≥8 weeks)	[redacted]	[redacted]
Progression	[redacted]	[redacted]

	Osimertinib (N=143)	Placebo (N=73)
Not evaluable	[redacted]	[redacted]
Comparison between groups		
Odds ratio (95% CI)§	[redacted]	
2-sided p-value¶	[redacted]	

†Response includes both confirmed and unconfirmed BICR responses; ‡Calculated using the Clopper-Pearson exact method for binomial proportions; §Based on the profile likelihood; ¶Based on the likelihood ratio test; ††Includes confirmed responses only (i.e., responses confirmed at least 4 weeks after the initial response).
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; ORR, objective response rate.
Source: Lu et al. (2024)[67] and CSR.[10]

Sensitivity analysis of ORR was repeated for the evaluable for response (EFR) analysis set and supported the results of the primary analysis of the ORR conducted on the FAS (OR: 2.76 [95% CI: 1.51, 5.14; nominal p<0.001]), which favoured the osimertinib arm (Table 18).

Table 18: Objective response by BICR (DCO 05 January 2024) (EFR)

Group	N	Number (%) of patients with response	95% CI†	Comparison between groups		
				Odds ratio	95% CI‡	2-sided p-value§
Sensitivity analysis of ORR¶						
Osimertinib	134	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	67	[redacted]	[redacted]			
Sensitivity analysis of ORR – confirmed responses††						
Osimertinib	134	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	67	[redacted]	[redacted]			

†Calculated using the Clopper-Pearson exact method for binomial proportions; ‡Based on the profile likelihood; §Based on the profile likelihood; ¶Response includes both confirmed and unconfirmed BICR responses; ††Confirmed responses were a subset of the responses (i.e., responses confirmed at least 4 weeks after the initial response).
Abbreviations: BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; EFR, evaluable for response; ORR, objective response rate.
Source: CSR.[10]

B.2.6.1.2.4 Duration of response (DCO 05 January 2024)

Duration of response (DoR) was defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression.

A clinically meaningful 30.4-month improvement in median DoR was observed with osimertinib (median DoR of 36.9 months) compared with patients who received placebo (median DoR of 6.5 months) (Table 19).

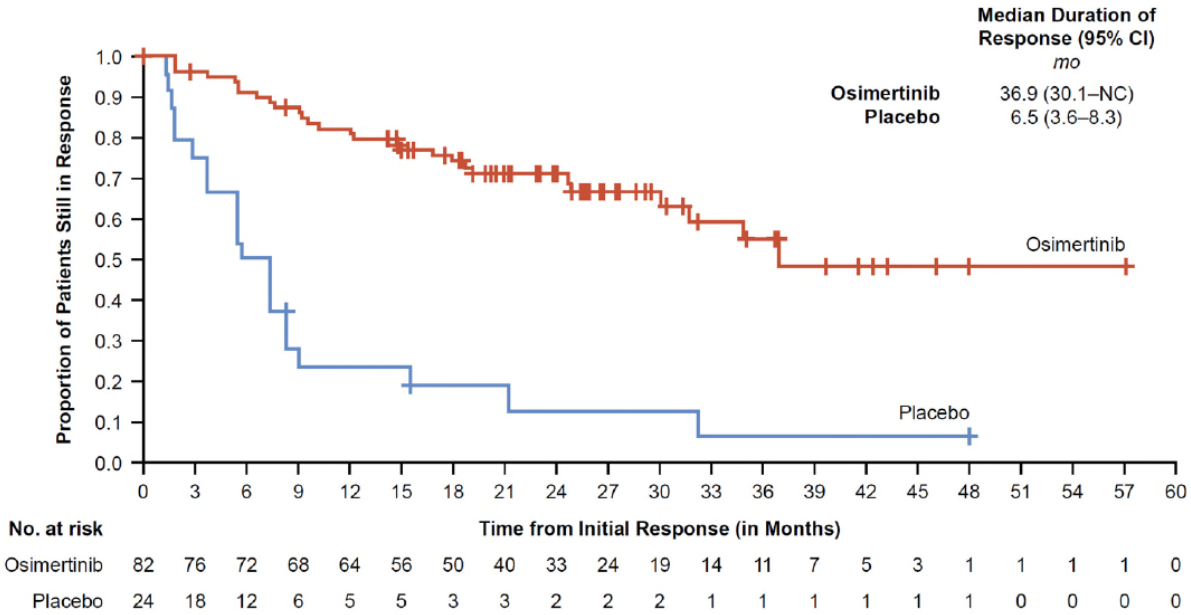
The KM curve of DoR by BICR also demonstrated early separation between treatment arms in favour of osimertinib, with the separation of curves sustained throughout the follow-up period (Figure 10).

Table 19: Duration of response by BICR (FAS)

	Osimertinib (N=143)	Placebo (N=73)
Analysis of DoR†		
Number of responders	82	24
Responders who subsequently progresses of died, n (%)	[redacted]	[redacted]
Median DoR, months (95% CI)‡	36.9 (30.1, NC)	6.5 (3.6, 8.3)
Time to onset of response, weeks†		
Mean (StD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Analysis of DoR – confirmed responses§		
Number of responders	[redacted]	[redacted]
Responders who subsequently progresses of died, n (%)	[redacted]	[redacted]
Median DoR, months (95% CI)‡	[redacted]	[redacted]

†Derived from unconfirmed responses only; ‡Calculated using KM technique; §Derived from confirmed responses only (i.e., responses confirmed at least 4 weeks after the initial response).
Abbreviations: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; DoR, duration of response; FAS, full analysis set; KM, Kaplan-Meier; NC, not calculable; StD, standard deviation
Source: Lu et al. (2024)[67] and CSR.[10]

Figure 10: Kaplan-Meier plot of DoR (unconfirmed) by BICR (FAS)



Abbreviations: BICR, blinded independent central review; DoR; duration of response; FAS, full analysis set.
Source: Lu et al. (2024).[67]

B.2.6.1.2.5 Disease control rate

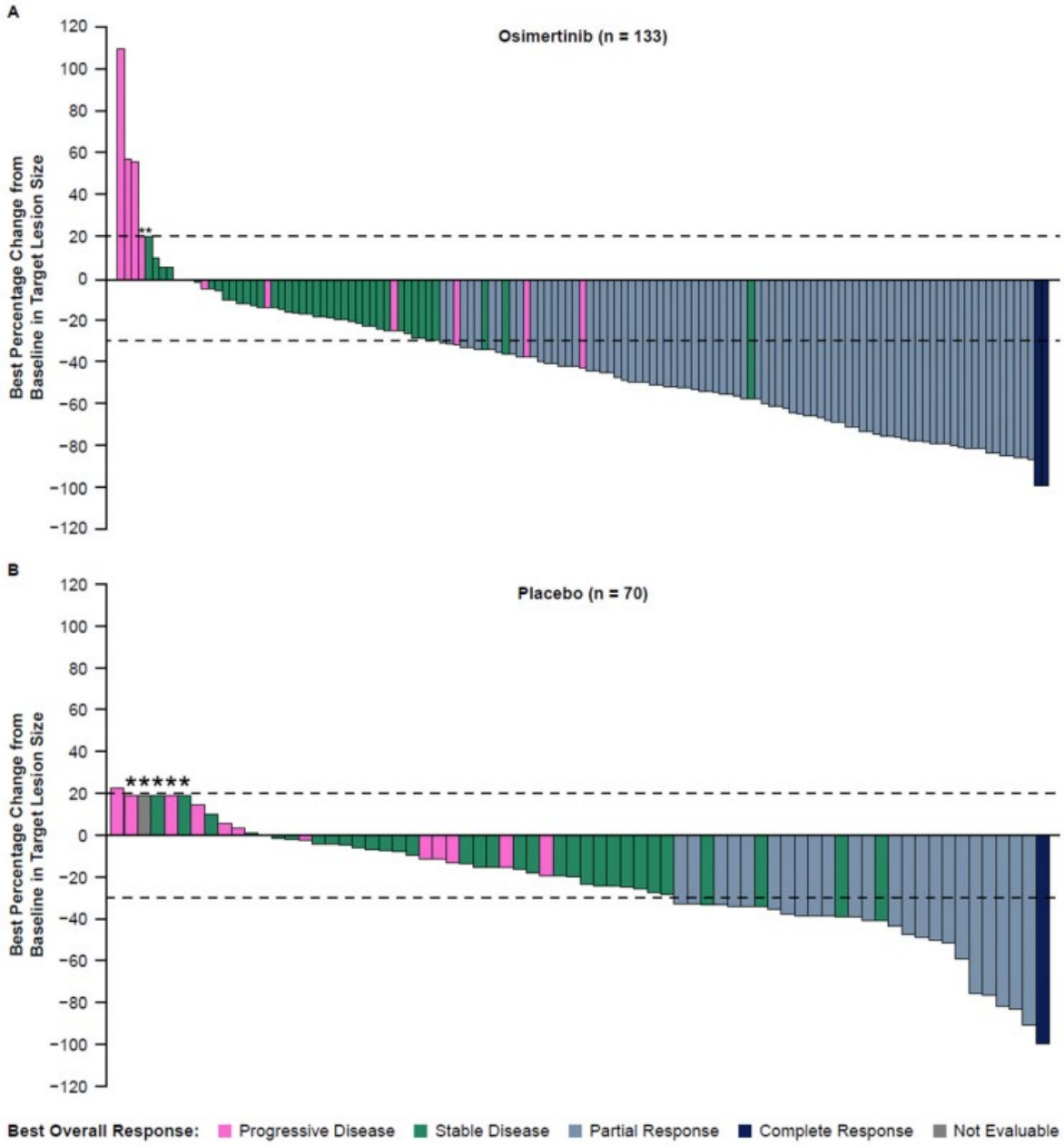
Disease control rate (DCR) was defined as the percentage of patients who had a best overall response (BoR) of CR or PR or SD at ≥ 8 weeks, prior to any progressed disease (PD) event.

A higher percentage of patients achieved disease control (a BoR of CR, PR or SD) in the osimertinib arm (88.8%; 95% CI: 82.5, 93.5) compared with the placebo arm (79.5%; 95% CI: 68.4, 88.0) with an odds ratio of 2.06 (95% CI: 0.94, 4.47).

B.2.6.1.2.6 Depth of response (tumour shrinkage) (DCO 05 January 2024)

An improvement in median tumour size and target lesion size from baseline was observed following treatment with osimertinib versus placebo (Figure 11).

Figure 11: Best percentage change from baseline in target lesions (FAS)



(A) Osimertinib group (B) Placebo group.
Asterisks indicate values imputed to 20%.
Abbreviations: FAS, full analysis set.
Source: Lu et al. (2024).[67]

Overall, the median best percentage change in target lesion size from baseline per BICR was observed in the osimertinib arm (43.3%) compared the placebo arm (21.9%), with a least square mean difference between arms of [redacted]% (95% CI: [redacted]; [redacted]).

A clinically meaningful ≥30% reduction in target lesion size from baseline based on BICR assessment was reported for [redacted]% of patients in the osimertinib arm compared with [redacted]% of patients in the placebo arm. A ≥50% reduction in target lesion size reported for [redacted]% of patients in the osimertinib arm and [redacted]% of patients in the placebo arm, while a ≥75% reduction in target lesion size was reported for [redacted]% of patients in the osimertinib arm and [redacted]% of patients in the placebo arm.

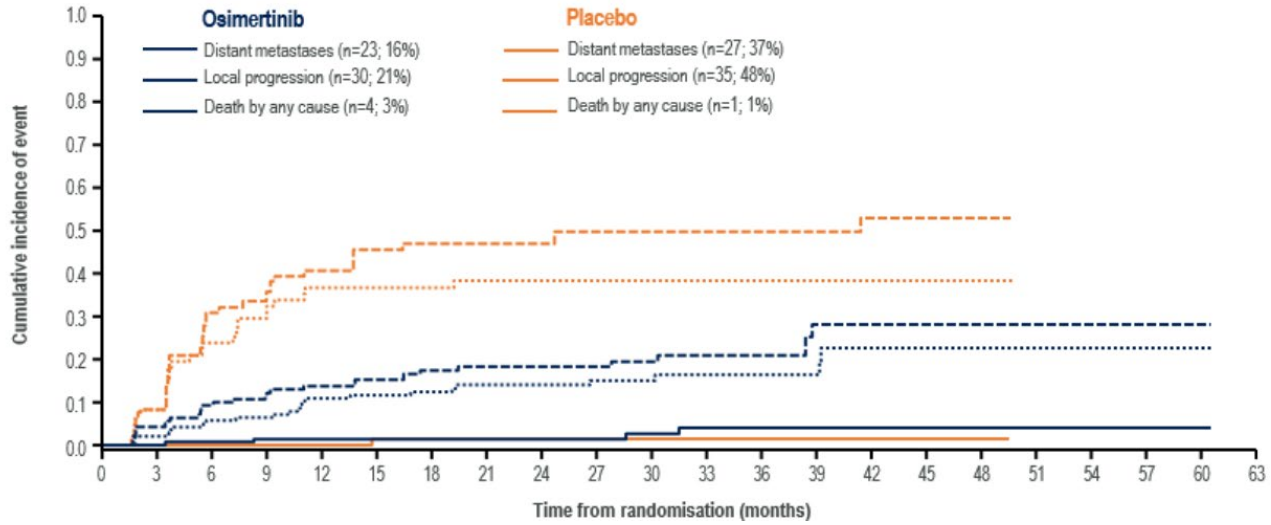
Waterfall plots presenting best percentage change from baseline in the sum of target lesion size by BICR assessment demonstrate that a higher proportion of patients in the osimertinib arm had a reduction in the sum of target lesions size from baseline, and a higher proportion of patients have a reduction of more than [redacted]% compared with patients in the placebo arm (Figure 11).

B.2.6.1.2.7 Time to death or distant metastases by BICR (DCO 05 January 2024)

Time to death or distant metastases was defined as the time from the date of randomisation until the first date of distant metastasis, or date of death in the absence of distant metastasis.

A clinically meaningful improvement in TTDM was observed in the osimertinib arm compared with placebo (HR: 0.21 [95% CI: 0.11, 0.38]; nominal p<0.001). Overall, the proportion of patients with a death or distant metastasis event in the osimertinib arm was approximately 2 times lower than in the placebo arm (33 patients [23.1%] versus 31 patients [42.5%], respectively) (Figure 12).

Figure 12: Cumulative incidence of death or distant metastases by BICR, competing risk analysis (FAS)



Distant metastases is defined as any new lesion that is detected on a scan (outside of the radiation field) according to RECIST v1.1 or proven by biopsy.
Abbreviations: BICR, blinded independent central review; CSR, clinical study report; FAS, full analysis set; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: Lu et al (2024).[70]

B.2.6.1.2.8 Time to treatment discontinuation or death (DCO 05 January 2024)

Time to treatment discontinuation or death (TTD) was defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death.

Treatment with osimertinib resulted in a clinically meaningful improvement in time to treatment discontinuation or death compared with placebo (HR: [redacted] [95% CI: [redacted]]; nominal [redacted] with a median TTD of [redacted] months (95% CI: [redacted]) in the osimertinib arm and [redacted] months (95% CI: [redacted] in the placebo arm.

B.2.6.1.3 Post-progression outcomes

B.2.6.1.3.1 Time to first subsequent therapy (DCO 05 January 2024)

Time to first subsequent therapy was defined as the time from the date of randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment, or death and can complement PFS results.[75] Time to first subsequent therapy was consistent with the PFS benefit observed (Section B.2.6.1.1.1).

A clinically meaningful longer median TFST was observed in patients receiving osimertinib compared with placebo ([redacted] months [95% CI: [redacted]] versus

[redacted]months [95% CI: [redacted]]), with a hazard ratio of [redacted] (95% CI: [redacted]nominal [redacted]) favouring the osimertinib arm. Overall, [redacted] patients ([redacted]%) in the osimertinib arm and [redacted] patients ([redacted]%) in the placebo arm had a TFST event, with an overall data maturity of [redacted]%.

The KM curve demonstrated early separation between treatment arms in favour of osimertinib (from approximately [redacted] months), which was sustained throughout the remainder of the follow-up period (Figure 13).

Figure 13: Kaplan-Meier plot of time to subsequent therapy (FAS)

[redacted]

Abbreviations: CI, confidence interval; CSR, clinical report study; FAS, final analysis set; HR, hazard ratio; NC, not calculable; TFST, time to first subsequent therapy.
Source: CSR.[10]

B.2.6.1.3.2 Second progression-free survival

Second progression-free survival was defined as the time from the date of randomisation to the earliest of the progression events following first objective disease progression, subsequent to the first subsequent therapy, or death. It has been shown to be an appropriate surrogate endpoint for OS.[76] A consistently significant improvement in second progression-free survival on a subsequent treatment (PFS2) was observed following treatment with osimertinib.

The HR for PFS2 was [redacted] (95% CI: [redacted]; nominal [redacted]), indicating a clinically meaningful improvement in PFS2 for patients in the osimertinib arm

compared with patients in the placebo arm. Overall, [redacted] patients ([redacted]%) in the osimertinib arm and [redacted] patients ([redacted]%) in the placebo arm had a PFS2 event, with an overall data maturity of [redacted]%.

A separation between treatment arms of the KM curves from approximately [redacted] months post-randomisation was observed in favour of the osimertinib arm, demonstrating continued clinical benefit beyond initial progression (Figure 14).

Median time to PFS2 was similar between the treatment arms (48.20 months [95% CI: 44.42, NC] in the osimertinib arm and 47.38 months [95% CI: 28.22, NC]) in the placebo arm). However, these medians were estimated based on a single event and should be interpreted with caution considering the limited number of patients who remained at risk at the tail of the KM curve (Figure 14).

Figure 14: Kaplan-Meier plot of second progression-free survival (FAS)

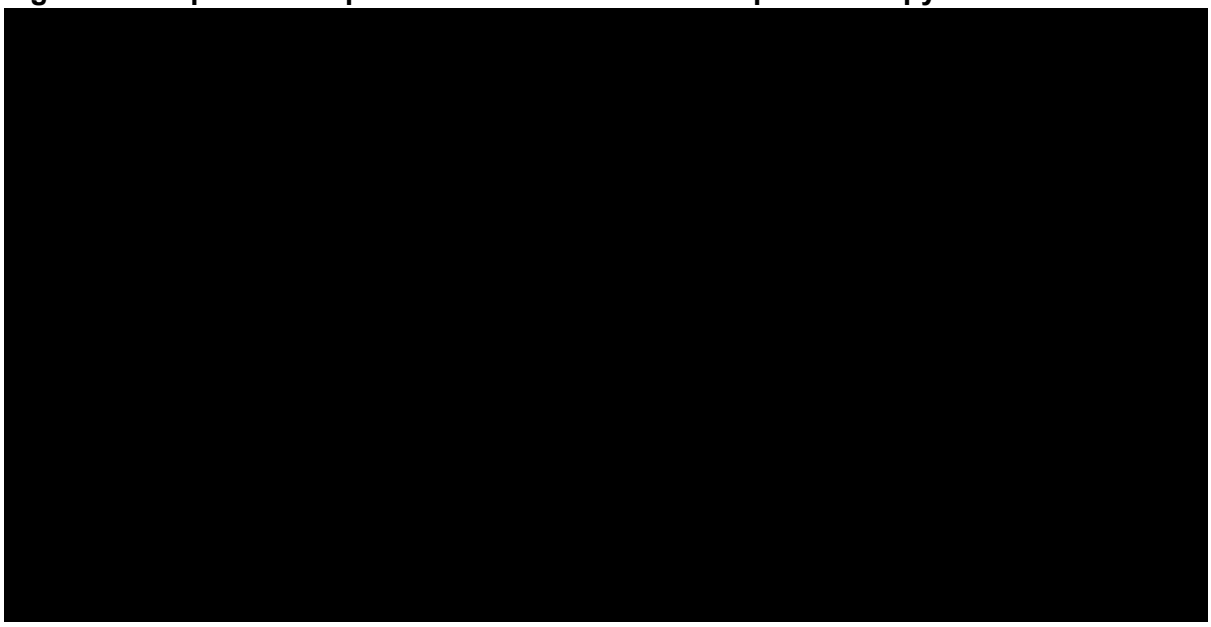
Abbreviations: CI, confidence interval; CSR, clinical study report; FAS, final analysis set; HR, hazard ratio; NC, not calculable; PFS2, second progression-free survival.
Source: CSR.[10]

B.2.6.1.3.3 Time to second subsequent treatment

Time to second subsequent treatment was defined as the time from the date of randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of randomised treatment, or death. Time to second subsequent treatment was consistent with the PFS2 benefit observed (Section B.2.6.1.3.2).

With a data maturity of [redacted]%, a clinically meaningful HR in favour of osimertinib was observed in relation to TSST (HR: [redacted] [95% CI: [redacted]]; nominal [redacted]), with the benefit of osimertinib observed from approximately [redacted] months post-randomisation which persisted throughout the remainder of the follow-up period (Figure 15). Overall, [redacted] patients ([redacted]%) in the osimertinib arm and [redacted] patients ([redacted]%) in the placebo arm had a TSST event.

Figure 15: Kaplan-Meier plot of time to second subsequent therapy



Abbreviations: CI, confidence interval; FAS, final analysis set; HR, hazard ratio; NC, not calculable; TSST, time to second subsequent therapy.
Source: CSR.[10]

B.2.6.1.4 Patient reported outcomes/quality of life

Patient reported outcomes were assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires.

Key outcomes assessed were as follows:

- Time to PRO symptom deterioration was analysed using the same methodology and model as for the primary analysis of PFS and is presented as a KM plot for each of the symptom scales and functional scales and HRQoL.

- Symptom improvement rate for each item from each questionnaire was compared by treatment arm using the same methodology and model as for the ORR analysis.
- Changes from baseline in each of the PRO symptom scores are analysed using a mixed models for repeated measures (MMRM) analysis of the post-baseline scores for visits with the use of data from baseline up to 10 months or date of PD (whichever is earlier), excluding visits with excessive missing data (defined as more than 75% missing data).

Patient reported outcome functioning and symptom subscales including global health status/HRQoL, appetite, dyspnoea, cough, chest pain, physical functioning or fatigue were assessed whereby, a clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 points.

B.2.6.1.4.1 Compliance

The overall compliance rate for the questionnaires were high (>[redacted]%) at the baseline for both treatment arms and remained high (>[redacted]%) until week 24, with rates comparable between treatment arms.

B.2.6.1.4.2 Baseline score

Baseline EORTC QLQ-C30 and EORTC QLQ-LC13 scores were comparable between treatment arms for all QLQ-C30 and QLQ-LC13 functional/symptom scales/items. In both treatment arms, patients had intermediate-to-high degrees of overall functioning and global health status/QoL (scores of ≥[redacted]) based on the QLQ-C30 questionnaire, with low or mild symptomatology (scores ≤[redacted]), based on data from both questionnaires.

B.2.6.1.4.3 Change from baseline

Overall, no clinically meaningful changes from baseline were observed for the functional/symptom scales/items of interest in both treatment arms, based on the MMRM analysis (Table 20).

Table 20: Summary of change from baseline in PRO domains and symptoms, MMRM (FAS)

PRO scale	Treatment arm	N	Estimate for treatment arm (95% CI)[†]	Comparison between groups	
				Estimate for difference	95% CI
EORTC QLQ-C30					
Global health status / QoL	Osimertinib Placebo	128 67	[redacted]	[redacted]	[redacted]
Physical function	Osimertinib Placebo	128 67	[redacted]	[redacted]	[redacted]
Fatigue	Osimertinib Placebo	128 67	[redacted]	[redacted]	[redacted]
Appetite loss	Osimertinib Placebo	128 67	[redacted]	[redacted]	[redacted]
EORTC QLQ-LC13					
Dyspnoea	Osimertinib Placebo	131 68	[redacted]	[redacted]	[redacted]
Coughing	Osimertinib Placebo	131 68	[redacted]	[redacted]	[redacted]
Pain in chest	Osimertinib Placebo	131 68	[redacted]	[redacted]	[redacted]

[†]Baseline is defined as the latest evaluable assessment on or prior to the day of first dose. The analysis is performed using a MMRM analysis of change from baseline score for all post-baseline assessments, with patient, treatment, visit and treatment-by-visit interaction as explanatory variables, the baseline score as a covariate along with the baseline score-by-visit interaction. Treatment, visit and treatment-by-visit interaction are fixed effects in the model and patient is included as a random effect. Restricted maximum likelihood estimation is used. An overall adjusted mean estimate to estimate the average treatment effect over visits is derived giving each visit equal weight. The treatment-by-visit interaction is kept in the model regardless of significance. Data are summarised up to the earlier of the date of progression or 10 months follow-up, excluding any visits with missing data that is ≥75% of patients at that visit.
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; FAS, full analysis; MMRM, mixed effect model for repeated measures; PRO, patient-reported outcome; QoL, quality of life.
Source: CSR.[10]

B.2.6.1.4.4 Time to deterioration

Overall, [redacted]% of patients in the osimertinib arm and [redacted]% of patients in the placebo arm did not experience a clinically meaningful deterioration in global health status/QoL or death based on EORTC QLQ-C30 questionnaire, with no meaningful difference in the risk of deterioration or death observed between treatment arms

(HR: [redacted] [95% CI: [redacted]]). No meaningful differences in the risk of deterioration between treatment arms were observed based on the HRs, and in all functional/symptom scales/items of interest, the proportion of patients without deterioration at 6 and 12 months was similar (<[redacted]% difference) between treatment arms, based on data from both questionnaires (Table 21).

Table 21: Analysis of time to confirmed deterioration in PRO domains and symptoms (FAS)

PRO Scales	Treatment arm	N	Number (%) of patients with events	Percentage (95% CI) of patients without deterioration†		Hazard ratio‡ (95% CI)
				At 6 months	At 12 months	
EORTC QLQ-C30						
Global health status / QoL	Osimertinib	131	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	68	[redacted]	[redacted]	[redacted]	
Physical Function	Osimertinib	130	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	68	[redacted]	[redacted]	[redacted]	
Fatigue	Osimertinib	130	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	68	[redacted]	[redacted]	[redacted]	
Appetite loss	Osimertinib	130	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	68	[redacted]	[redacted]	[redacted]	
EORTC QLQ-LC13						
Dyspnoea	Osimertinib	131	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	68	[redacted]	[redacted]	[redacted]	
Coughing	Osimertinib	130	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	67	[redacted]	[redacted]	[redacted]	
Pain in chest	Osimertinib	131	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	68	[redacted]	[redacted]	[redacted]	

†Calculated using the KM technique; ‡The analysis includes patients with non-missing baseline scores of ≥ 10 (for GHS/QoL and functioning) or ≤ 90 (for symptoms) and was performed using a log-rank test stratified by disease stage prior to chemoradiation (IIIA versus IIIB/IIIC) based on values entered into the IxRS. A HR < 1 favours osimertinib.
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items; FAS, full analysis; GHS, global health status; HR, hazard ratio; KM, Kaplan-Meier; PRO, patient-reported outcome; QoL, quality of life.
Source: CSR.[10]

B.2.6.1.4.5 Exploratory endpoints

Mean value for Visual Analogue Scale (VAS) score >76 was observed for both treatment arms at baseline and also generally maintained over time.

At baseline, VAS mean scores were comparable between treatment arms and the percentage of patients reporting “No Problem” for each EQ-5D-5L domains was higher than for all the other response levels (presented in Section B.3.4).

B.2.6.1.5 Efficacy conclusions

The unprecedented results of the LAURA study demonstrated that treatment with osimertinib significantly reduced the risk of progression to metastatic disease, showed a positive trend in OS (with final analysis to be caried out at ~60% data maturity) and revealed a nominally statistically significant reduction in CNS metastases. The use of osimertinib in locally advanced unresectable NSCLC following CRT will be practice changing for clinicians as it will be the first targeted treatment for EGFRm patients in this setting.

Osimertinib delivered a statistically significant and clinically meaningful 84% reduction in the risk of disease progression or death compared with placebo (HR: 0.16 [95% CI: 0.10, 0.24]; p<0.001). Moreover, treatment with osimertinib resulted in an unprecedented 33.6-month improvement in median PFS, a seven-fold increase compared with placebo, with early separation of curves from the first RECIST scan at 8 weeks in favour of the osimertinib arm for the entire duration of the follow-up. Clinical experts consulted as part of an advisory board stated that the PFS results for osimertinib are practice changing.[15]

At the interim OS analysis data was immature (19.9%), with an initial positive trend towards improved OS with osimertinib versus placebo (HR: 0.81 [95% CI: 0.42, 1.56]; p=0.530) and should be interpreted in the context of the substantial degree of crossover, as 50 patients (80.6%) in the placebo arm received osimertinib following BICR-confirmed disease progression at the DCO of the interim analysis. Despite the immaturity of OS data, the post-progression endpoints of TFST, PFS2 and TSST indicated that the PFS benefit was largely sustained through subsequent lines of

therapy, supporting the long-term benefits of osimertinib for patients with locally advanced unresectable EGFRm NSCLC.

Osimertinib also delivered a nominally statistically significant and clinically meaningful 83% reduction in the risk of CNS progression or death compared with placebo (HR: 0.17 [95% CI: 0.09, 0.32], nominal p<0.001). There was a clinically meaningful 79% reduction in the risk of distant metastases or death (HR: 0.21 [95% CI: 0.11, 0.38]; nominal p< 0.001).

Furthermore, a clinically meaningful incremental [redacted]% improvement in ORR was observed in favour of osimertinib treatment, and a durable 30.4-month improvement versus placebo in median DoR was reported for all patients with BICR-assessed responses.

The efficacy benefits of osimertinib were delivered with no clinically meaningful deterioration in HRQoL; there was no clinically meaningful difference in the risk of deterioration across all EORTC QLQ-LC13 and EORTC QLQ-30 scales between the osimertinib and placebo groups. The results of LAURA demonstrate that treatment with osimertinib provides an important benefit for patients with advanced EGFRm (Ex19del and/or L858R) NSCLC whose disease has not progressed after platinum-based CRT.

B.2.7 Subgroup analysis

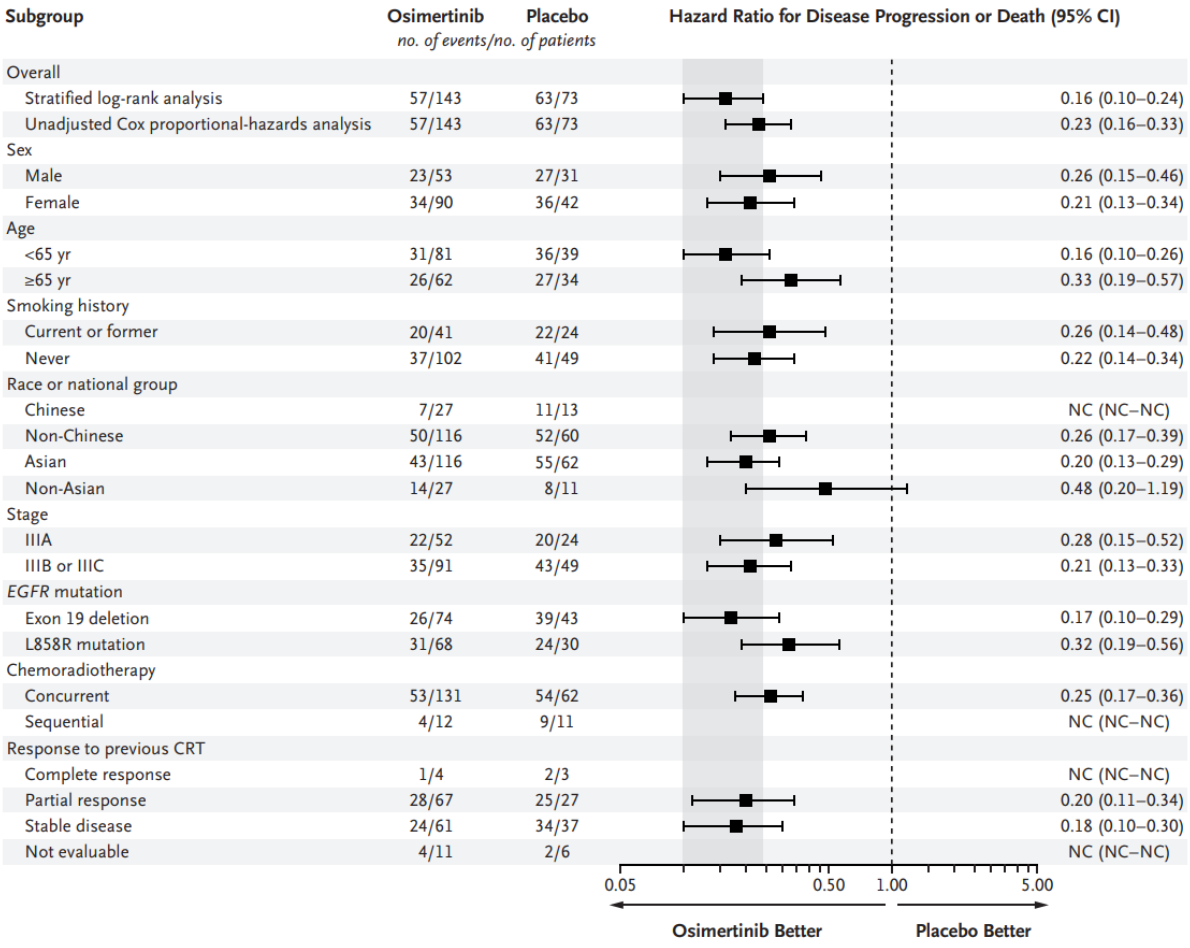
Pre-planned subgroup analyses included age (<65 versus ≥ 65 years), sex, smoking history (current/former versus no), race (Asian versus non-Asian), China cohort, disease stage (IIIA vs IIIb/IIIC), prior CRT (concurrent/sequential), response to prior CRT, and EGFR mutation type (Ex19del or L858R) (Figure 16). Progression-free survival was analysed for the pre-specified subgroups, using a Cox-proportional hazards model containing a term for treatment, the factor of interest and treatment-by-factor interaction term; the Efron method was used to handle ties.

Results were presented as a hazard ratio with associated 95% CI for all subgroups with sufficient events for analysis (≥20 events across both treatment groups). No

adjustment to the significance level was made since the purpose of these subgroup analyses was to assess the consistency of treatment effect of progression-free survival by BICR across the pre-specified subgroups, to support the primary analysis of progression-free survival.

The PFS benefit observed in the osimertinib arm (DCO 05 January 2024) was consistently seen in all pre-specified subgroups. A hazard ratio of <0.3 was reported for the majority of pre-specified subgroups, corresponding to a clinically meaningful reduction in the risk of disease progression or death.

Figure 16: Subgroup analysis of progression-free survival by BICR (FAS)



Abbreviations: BICR, blinded independent central review; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation positive; Ex19del, exon 19 deletion; FAS, full analysis set; HR, hazard ratio; L858R, an amino acid substitution at position 858 in EGFR, from a leucine (L) to an arginine (R); PH, proportional hazard; SCRT, sequential chemoradiotherapy.
Source: Lu et al (2024).[67]

B.2.8 Meta-analysis

LAURA is the only Phase 3 RCT reporting on the efficacy and safety of osimertinib in patients with locally advanced, unresectable EGFRm NSCLC, therefore a meta-analysis was not required.

B.2.9 Indirect and mixed treatment comparisons

No further studies other than LAURA that were deemed relevant to the decision problem were identified in the SLR for patients with locally advanced, unresectable EGFRm NSCLC. As the only relevant comparator for the submission is BSC, an indirect or mixed-treatment comparison was not deemed necessary.

B.2.10 Adverse reactions

Osimertinib has a tolerable safety profile, low treatment discontinuation rates, with the types of AEs reported being reflective of the known toxicities and established safety profiles of osimertinib.

The LAURA AE analyses presented in this section were conducted based on the safety analysis set (SAS), which consisted of 143 patients who received at least one dose of osimertinib, and 73 patients who received at least one dose of placebo. The analyses of AEs presented comprise those events with an onset date on or after the date of the first dose of study treatment, up to and including the 28-day follow-up period, or the day before administration of any subsequent anticancer therapies. Adverse event data were evaluated according to the following categories: All AEs (including those causally related to study treatment), AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher, AEs with an outcome of death, all serious adverse events (SAEs), AEs leading to treatment discontinuation, and AEs leading to dose modification.

B.2.10.1 Exposure

At the DCO date of 05 January 2024, the total median exposure to study treatment was notably higher in the osimertinib arm (23.98 months) compared with the placebo arm (8.31 months) (Table 22). The actual median exposure in the osimertinib arm

was almost identical to the total median exposure (23.69 months versus 23.98 months, respectively (Table 22), indicating that dosing interruptions did not have a meaningful impact on overall exposure to osimertinib.

Table 22: Extent of exposure (SAS)

	Osimertinib (N=143)	Placebo (N=73)
Total exposure (months)†		
N	143	73
Mean (StD)	[redacted]	[redacted]
Median	23.98	8.31
Min, max	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]
Actual exposure (months)‡		
N	143	73
Mean (StD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]

†Total treatment duration = (last dose date - first dose date + 1) / (365.25/12); ‡Actual treatment duration = total treatment duration, excluding dose interruptions.
Abbreviations: CSR, clinical study report; SAS, safety analysis set; StD, standard deviation.
Source: CSR.[10]

B.2.10.2 Adverse event overview

At the DCO of 05 January 2024 a total of 140 patients (97.9%) treated with osimertinib reported an AE, the majority of which were non-serious, mild or moderate in severity, and did not lead to treatment discontinuation (Table 23). The majority of patients in the placebo arm (64 patients [87.7%]) also experienced at least one AE. The proportion of patients that experienced an AE reported as possibly related to treatment was higher in the osimertinib arm (80.4%) compared with the placebo arm (41.1%). Other types of AEs which were higher in the osimertinib arm compared with the placebo arm included Grade ≥3 AEs (35.0% vs 12.3%), SAEs (38.5% vs 15.1%), AEs leading to discontinuation of the study treatment (12.6% vs 5.5%), and AEs leading to dose modifications (55.9% vs 24.7%). The proportions of patients who had

an AE with outcome of death were low in both treatment arms (2.1% in the osimertinib arm and 2.7% in the placebo arm).

Table 23: Overview of adverse events (SAS)

AE category	Osimertinib (N=143)		Placebo (N=73)	
	Number (%) of patients†	Patient rate (per 100 pt years)‡	Number (%) of patients†	Patient rate (per 100 pt years)‡
Any AE	140 (97.9)	[redacted]	64 (87.7)	[redacted]
Any AE possibly related to treatment§	[redacted]	[redacted]	[redacted]	[redacted]
Any AE of CTCAE Grade ≥3¶	50 (35.0)	[redacted]	9 (12.3)	[redacted]
Any AE of CTCAE Grade ≥3 possibly related to treatment§, ¶	[redacted]	[redacted]	[redacted]	[redacted]
Any AE with an outcome of death	[redacted]	[redacted]	[redacted]	[redacted]
Any AE with an outcome of death possibly related to treatment§	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE possibly related to treatment§	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation of treatment	18 (12.6)	[redacted]	4 (5.5)	[redacted]
Any AE leading to discontinuation of treatment possibly related to treatment§	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to dose modification	80 (55.9)	[redacted]	18 /(24.7)	[redacted]
Any AE leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to dose interruption	[redacted]	[redacted]	[redacted]	[redacted]

† Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories; ‡ Number of patients with AEs divided by the total duration of treatment across all patients in given group, multiplied by 100. The total duration of treatment across all patients in osimertinib = 282.54 years; in placebo = 71.63 years; § As assessed by the investigator; ¶Includes any AEs with an unknown CTCAE Grade (where applicable).
Abbreviations: AE, adverse event; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; pt, patient; SAE, serious adverse event.
Source: CSR.[10]

B.2.10.3 Most common AEs

The most frequently reported AEs in both treatment arms at the DCO of 05 January 2024 were radiation pneumonitis (48% with osimertinib versus 38% with placebo), diarrhoea (36% with osimertinib versus 14% with placebo), and rash (24% with osimertinib versus 14% with placebo) (Table 24). These are adverse drug reactions

which are to be expected for a population of patients who had received prior CRT (radiation pneumonitis) or osimertinib treatment (diarrhoea and rash).

Table 24: Adverse events by preferred term occurring in ≥5% of patients in either treatment arm (SAS)

Preferred term	Number (%) of patients	
	Osimertinib (N=143)	Placebo (N=73)
Patients with any AE	140 (98)	64 (88)
Radiation pneumonitis	68 (48)	28 (38)
Diarrhoea	51 (36)	10 (14)
Rash	34 (24)	10 (14)
COVID-19	29 (20)	6 (8)
Paronychia	24 (17)	1 (1)
Cough	23 (16)	7 (10)
Decreased appetite	21 (15)	4 (5)
Dry skin	18 (13)	4 (5)
Pruritis	18 (13)	5 (7)
Stomatitis	17 (12)	2 (3)
White blood cell count decreased	17 (12)	2 (3)
Pneumonia	16 (11)	6 (8)
Anaemia	14 (10)	3 (4)
Herpes zoster	13 (9)	2 (3)
Urinary tract infection	11 (8)	2 (3)
ALT level increased	10 (7)	2 (3)
Arthralgia	10 (7)	6 (8)
Upper respiratory tract infection	10 (7)	1 (1)
Acneiform dermatitis	9 (6)	2 (3)
Platelet count decreased	8 (6)	0
Dyspnea	8 (6)	5 (7)
AST level increased	8 (6)	1 (1)
Nasopharyngitis	8 (6)	0
Pneumonitis	8 (6)	1 (1)
Sinus tachycardia	8 (6)	1 (1)
Productive cough	7 (5)	4 (5)
Musculoskeletal chest pain	5 (3)	9 (12)
Myalgia	5 (3)	6 (8)
Headache	2 (1)	4 (5)

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.
Source: Lu et al. (2024).[67]

B.2.10.4 Adverse events by severity

At the DCO of 05 January 2024, of the majority of patients ([redacted]% in the osimertinib arm and [redacted]% in the placebo arm) reported AEs that were maximum CTCAE Grade 1 (mild) and 2 (moderate) (Table 25). Few patients reported life-threatening AEs with a maximum severity of CTCAE Grade 4 in both treatment arms ([redacted]% of patients in the osimertinib arm and [redacted]% of patients in the placebo arm). An increase in the incidence of CTCAE Grade ≥3 AEs in the osimertinib arm was expected as these patients had a longer exposure to osimertinib treatment compared with the placebo arm.

Table 25: Summary of AEs by maximum reported CTCAE grade (SAS)

Maximum reported CTCAE grade	Number (%) of patients	
	Osimertinib (N=143)	Placebo (N=73)
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Event; SAS, safety analysis set.
Source: CSR.[10]

Overall, CTCAE Grade ≥3 AEs were reported by 50 patients (35.0%) in the osimertinib arm and 9 patients (12.3%) in the placebo arm. The most common CTCAE Grade ≥3 AEs reported in the osimertinib arm were pneumonia (2.8%), radiation pneumonitis (2.1%), and diarrhoea (2.1%) (Table 26).

Table 26: Summary of CTCAE Grade ≥3 AEs by preferred term occurring in ≥2% of patients in either treatment arm (SAS)

Preferred term	Number (%) of patients	
	Osimertinib (N=143)	Placebo (N=73)
Patient with any CTCAE Grade ≥3 AE	50 (35.0)	9 (12.3)
Pneumonia	4 (2.8)	3 (4.1)
Radiation pneumonitis	3 (2.1)	0
Diarrhoea	3 (2.1)	0
Gastroenteritis	2 (1.4)	0
Pneumonitis	2 (1.4)	0
Blood creatinine phosphokinase increased	2 (1.4)	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Event; SAS, safety analysis set.
Source: CSR.[10]

B.2.10.5 Safety overview

Treatment with osimertinib demonstrated a manageable safety and tolerability profile in the target patient population. The types of AEs reported were reflective of the known toxicities and established safety profiles of osimertinib. The majority of AEs were non-serious, mild or moderate in severity and did not lead to permanent osimertinib discontinuation, and rates of treatment discontinuation were low ([redacted]% in the osimertinib arm and [redacted]% in the placebo arm), demonstrating that osimertinib treatment was well tolerated.

B.2.11 Ongoing studies

LAURA is currently ongoing. The final OS analysis will be conducted when the data are approximately 60% mature (currently anticipated to be [redacted]). AstraZeneca are sponsoring an ongoing global RWE study, LEROS,[77] which is evaluating treatment patterns and clinical outcomes in patients with unresectable EGFRm NSCLC treated with CRT. However this study did not meet the inclusion criteria for the SLR as real-world studies were excluded.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Summary of clinical trial evidence

The efficacy and safety of osimertinib in patients with locally advanced, unresectable NSCLC with centrally confirmed EGFRm (Ex19del and/or L858R), whose disease has not progressed during or following definitive platinum-based CRT was demonstrated by the LAURA study.

The results of the LAURA study support the positioning of osimertinib after CRT in the locally advanced, unresectable setting. There are currently no treatment options in this setting and the LAURA study demonstrates that osimertinib can significantly delay disease progression and improve patient outcomes when used in this setting. The primary objective of the LAURA study was PFS by BICR. This objective was met by demonstrating an unprecedented statistically significant and clinically meaningful 84% reduction in the risk of disease progression or death with osimertinib compared with placebo (HR: 0.16 [95% CI: 0.10, 0.24]; p<0.001). This represents a seven-fold improvement in PFS. Analysis of PFS by BICR was consistent with the investigator-based analysis, with a 33.6-month improvement in median PFS observed in the osimertinib arm compared with the placebo arm (median PFS: 39.1 months vs 5.6 months, respectively). The PFS benefit in the osimertinib arm compared with the placebo arm was consistently observed across all prespecified subgroup analyses. Treatment with osimertinib also demonstrated a nominally statistically significant and clinically meaningful 83% reduction in the risk of CNS progression or death compared with placebo (HR: 0.17 [95% CI: 0.09, 0.32; p<0.001]).

At the interim OS analysis (05 January 2024), the data had reached 19.9% maturity and there was a favourable trend towards improved OS with osimertinib versus placebo (HR: 0.81 [95% CI: 0.42, 1.56]. Median OS in the osimertinib arm was 54.0 months (95% CI: 46.5, NC) and was not reached in the placebo arm. Despite the data being immature, an OS benefit is anticipated by UK clinicians.[15] It also should

be noted that the median OS for osimertinib was estimated based on a single event with few patients at risk and therefore should be interpreted with caution at this point. Moreover, all patients were offered open-label osimertinib following BICR-confirmed disease progression due to unprecedented efficacy, with 50 patients (80.6%) in the placebo arm receiving osimertinib following BICR-confirmed disease progression at the DCO of the interim analysis, therefore the results of OS at the current DCO date should be interpreted in the context of the substantial degree of crossover to osimertinib treatment post-BICR-confirmed progression in the placebo arm, which is likely to extend survival beyond what would be expected for patients treated with placebo.

Higher response rates were observed in the osimertinib arm compared with the placebo arm ([redacted]% versus [redacted]%, respectively), with a statistically significant odds ratio of 2.77 (95% CI: 1.54, 5.08; nominal p<0.001) in favour of osimertinib, and a clinically meaningful 30.4-month improvement in median DoR was also observed in the osimertinib arm compared with the placebo arm. A clinically meaningful improvement in TTDM was observed in the osimertinib arm compared with placebo (HR: 0.21 [95% CI: 0.11, 0.38]; nominal p<0.001), with patients in the osimertinib arm having a 2 times lower risk of death or distant metastasis compared with the placebo arm. [redacted], with a clinically meaningful longer median TFST (HR: [redacted] (95% CI: [redacted]; nominal [redacted]) and TSST (HR: [redacted] [95% CI: [redacted]]; nominal [redacted]) in patients receiving osimertinib compared with placebo, thus supporting the long-term benefits of osimertinib.

The efficacy benefits of osimertinib were delivered with no clinically meaningful deterioration in HRQoL; there was no significant difference in the risk of deterioration across all EORTC QLQ-LC13 and EORTC QLQ-30 scales between the osimertinib and placebo arms.

The safety profile of osimertinib in LAURA was consistent with its well-established safety profile in other NSCLC indications,[11] with no new clinically relevant toxicities or AEs reported in this setting. The most frequently reported AEs were expected for

a population of patients who had prior CRT and were receiving osimertinib. The majority of AEs in the osimertinib arm were non-serious, mild or moderate in severity, and the rates of treatment discontinuation were low ([redacted]% in the osimertinib arm and [redacted]% in the placebo arm) demonstrating that osimertinib treatment was well tolerated.

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

Strengths

LAURA is the first phase 3 trial to demonstrate the benefit of an EGFR-TKI after CRT in the locally advanced unresectable setting. The trial demonstrates that osimertinib can significantly delay progression to metastatic disease resulted in a nominally significant reduction the incidence of CNS metastasis when given after CRT. Clinical experts consulted as part of an advisory board stated that the PFS results for osimertinib are practice changing.[15]

LAURA is an international, multicentre, well-controlled and well-conducted study which employed a double-blind and randomised design to minimise risk of bias. LAURA utilised a placebo control arm; as there are currently a lack of alternative treatment options for patients with locally advanced, unresectable EGFRm NSCLC,[78] placebo as a proxy for BSC was appropriate for UK clinical practice.

The use of osimertinib in the LAURA trial reflects the proposed indication and anticipated use of osimertinib as treatment for patients with locally advanced, unresectable (stage III) NSCLC with EGFRm (EGFR exon 19 deletions or exon 21 [L858R] substitution mutations) whose disease has not progressed during or following platinum-based CRT in England. The trial dosing for osimertinib in LAURA matches the expected licensed indication and its use in UK clinical practice.

The study population and disease characteristics were well balanced across treatment arms. The median age of randomised patients was 62.5 years, with more female than male patients (61.1% versus 38.9%), more never-smokers (69.9%), and 82.4% of patients of Asian ethnicity. Epidermal growth factor receptor gene

mutations are more common in Asian patients, women, and never-smokers, therefore the demographics of the study conformed to the expected demographic and patient characteristics of patients with locally advanced unresectable EGFRm NSCLC. Clinicians consulted as part of an advisory board agreed that the results of the LAURA trial are expected to be generalisable to patients with locally advanced, unresectable EGFRm NSCLC in England.[15]

Patients were stratified at randomisation based on the potential prognostic factors of prior CRT strategy and disease stage prior to CRT, and upon review, the proportion of patients who had received prior CCRT versus SCRT (89.4% versus 10.6%, respectively) was reflective of UK clinical practice.[15]

A substantial proportion of study recruitment and conduct took place during and following the COVID-19 pandemic, and therefore the impact of the pandemic was thoroughly evaluated in terms of both efficacy and safety. The results of these evaluations did not suggest any influence of COVID-19 on the conduct of the study and overall, the COVID-19 pandemic was not judged to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of results.

Treatment with osimertinib resulted in unprecedented statistically significant and clinically meaningful improvements in PFS compared with placebo in the LAURA study and thus the trial met its primary endpoint. Progression-free survival was considered the most appropriate endpoint for LAURA, as a well-established clinical outcome, relevant to the oncology setting. Progression was defined according to RECIST 1.1, which is the well-recognised international standard for measurement of tumour burden.[73] Compared with OS, PFS can be measured over a shorter follow-up and is not affected by crossover or confounding due to later lines of therapy and therefore directly reflects the impact of the treatment effect under consideration. The use of PFS as a primary endpoint is particularly relevant in settings such as the locally advanced, unresectable setting where OS maturity takes a long time to achieve, and patients have a poor prognosis with access to limited effective treatments. The European Medicines Agency (EMA) allows PFS to be selected as

the primary endpoint for cancers, normally requiring OS to be reported as a secondary endpoint.[73] However, in situations where there is a substantial treatment effect on PFS, or where there is an expected long period of survival after progression, precise estimate of OS may not be required for EMA approval.[73] For example, the FLAURA trial supported the regulatory approval and subsequent reimbursement of osimertinib monotherapy in NSCLC and the establishment of this treatment regimen as SoC across many markets with PFS as a primary endpoint, supported by OS as a secondary endpoint.[79]

In addition, the post-progression endpoints of [redacted], supporting the long-term survival benefit of osimertinib for patients with locally advanced unresectable EGFRm NSCLC.

UK clinicians stated that the LAURA trial was well executed with impressive results and immediately practice changing. [15]

Limitations

The main limitation of LAURA is the immaturity of OS data, with 19.9% events having occurred at the primary PFS analysis DCO date (05 January 2024). Whilst an initial positive trend favouring osimertinib was observed, the difference was not statistically significant and the full survival benefit of osimertinib is yet to be established. The OS results should also be interpreted in the context of the low number of events and substantial crossover to osimertinib following BICR-confirmed disease progression in the placebo arm (80.6% of patients in the placebo arm switched to open-label osimertinib following disease progression). However, the [redacted], supporting the long-term survival benefit of osimertinib for patients with locally advanced unresectable EGFRm NSCLC.

During an advisory board, clinicians raised the lack of PET scanning in patients who received prior CCRT in the LAURA trial, as this is part of routine clinical practice in

the UK. PET scans were recommended but were not mandatory during the LAURA trial. The implications of this could lead to a risk of misclassifying the stage of disease, potentially leading to inappropriate treatment decisions, difficulties in assessing the true effectiveness of osimertinib in the trial population, and generalisability of the findings to UK clinical practice.[15] Despite clinician concerns, the PFS benefit with osimertinib vs placebo was consistent with or without pre-CRT staging by PET scan, and consistent with the primary PFS data in LAURA (HR [95% CI]: 0.24 [0.14, 0.40] for patients who received a PET scan versus HR [95% CI] 0.23 [0.13, 0.38] for patients who did not receive a PET scan.[70] These data were reassuring to clinicians as stated in the advisory board.[15]

Moreover, some of the clinicians stated that the outcomes of patients randomised to the control arm who received prior CRT followed by placebo were poorer than expected in UK clinical practice.[15] However, a previous study has shown that unresectable EGFRm NSCLC patients receiving CCRT have significantly worse median PFS compared with wtEGFR patients (9.8 vs 16.5 months, respectively).[72]

Discussion on clinical evidence

Maintaining stable disease and delaying progression from locally advanced to metastatic disease is a key treatment goal for patients with unresectable advanced NSCLC. In the post-CRT setting, patients with unresectable advanced EGFRm NSCLC lack targeted treatment options, with management currently consisting of BSC (active monitoring only).

Unresectable EGFRm NSCLC patients are at high risk of disease progression with approximately 70% of patients developing recurrence or metastasis within 2 years of receiving CRT.[4-6] Progression from advanced to metastatic disease is associated with a dramatically reduced 5-year survival rate from 25% in locally advanced disease to 9% in metastatic disease).[23] Furthermore, progression to metastatic NSCLC is also associated with a substantial increase in disease symptoms and a significant reduction in QoL.[26-28, 80] In particular, patients with EGFRm NSCLC have nearly double the risk of developing CNS metastases compared with wild-type EGFR

NSCLC patients (70% vs 38%) which are associated with a decline in neurological and cognitive function, complex symptoms, and limited life expectancy.[52, 53]

The findings of LAURA demonstrate that osimertinib addresses the significant unmet need in this population, providing a statistically significant and clinically meaningful 84% reduction in the risk of disease progression or death and an unprecedented 33.6-month improvement in median PFS compared with placebo. Osimertinib treatment also delivered a nominally statistically significant and clinically meaningful 83% reduction in the risk of CNS progression or death compared with placebo. Most CNS PFS events observed were due to new CNS lesions; however, the proportion of patients with new CNS lesions was 3 times lower following treatment with osimertinib compared to placebo (11.9% vs. 35.6%). According to UK clinicians consulted as part of an advisory board, the LAURA trial results were considered to be practice-changing, with the specialists recognising the CNS protection and PFS benefits of osimertinib. Furthermore, they stated that the results of the LAURA trial provide a strong evidence base to support the integration of osimertinib in treatment protocols for EGFRm patients post-CRT.[15]

Although OS data are currently immature, the [redacted] and support the long-term benefits of osimertinib. The efficacy benefits of osimertinib were delivered with no clinically meaningful deterioration in HRQoL compared with placebo, as measured using the EORTC QLQ-LC13 and EORTC QLQ-30 scales. Furthermore, osimertinib was well-tolerated, with a safety profile consistent with its known profile across other NSCLC indications.

The evidence from the LAURA study therefore demonstrates that osimertinib represents an important advancement in the management of locally advanced unresectable EGFRm NSCLC, addressing a substantial unmet need for patients who currently have no treatment options that can delay progression to metastatic disease following CRT.

B.3 Cost effectiveness

- A cost-effectiveness analysis was conducted to compare osimertinib with placebo (as a proxy for BSC) for the treatment of patients with locally advanced, unresectable, EGFRm NSCLC whose disease did not progress during or following platinum-based doublet CRT. This is consistent with the population and comparators in the LAURA trial and the anticipated marketing authorisation for osimertinib
- The analysis was consistent with the NICE reference case and took an NHS and Personal Social Services (PSS) perspective. Costs and benefits were discounted at a rate of 3.5% and evaluated over a lifetime horizon (38.6 years)
- A semi-Markov state transition model with three health states was used. These were progression-free (PF), progressed disease (PD) and death
- Costs in the model included treatment acquisition and administration, subsequent treatments, treatment of AEs, health care resource use, CNS metastases and end-of-life care
- Health state utility values were based on LAURA and FLAURA (the pivotal trial for osimertinib for first-line treatment of adult patients with locally advanced or metastatic NSCLC), and the model accounted for disutilities related to Grade 3 and 4 AEs
- In the base case analysis, the ICER was £20,316 per QALY gained for osimertinib versus placebo with incremental total costs of [redacted] and incremental QALYs of [redacted]
  - For this analysis, the confidential price of osimertinib (a pack of 30, 80 mg tablets) was used, consistent with the commercial access agreement for osimertinib with NHS England.
- The mean ICER resulting from the probabilistic analyses [redacted] with respect to parameter uncertainty. At a WTP threshold of £30,000 per QALY gained, the probability of osimertinib being cost-effective versus placebo is 87.8%
- Scenario analyses that resulted in the lowest and highest ICERs are:

- Using lognormal to extrapolate TTP and PFS: £14,162
- Removing the cap for TTD application in the model: £25,249

- Deterministic sensitivity analysis indicated that the other most influential parameters on the ICER are the health state utility values for progression-free and progressed disease, the proportion of patients in the placebo arm who subsequently receive osimertinib and the proportion of patients receiving placebo as a first line therapy, resulting in a range of ICERs between £16,311 and £24,259 per QALY gained
- Further to the important demonstrated clinical benefits such as the unprecedented PFS benefit and delay in CNS disease progression versus placebo in the LAURA trial, osimertinib has been demonstrated to be a cost-effective treatment option for patients with locally advanced, unresectable, EGFRm NSCLC which has not progressed during or following definitive platinum-based CRT

B.3.1 Published cost-effectiveness studies

B.3.1.1 Identification of studies

An SLR was conducted to identify published cost-effectiveness evidence following chemoradiation in unresectable locally advanced NSCLC, including evidence relating to costs and healthcare resource use.

Electronic databases were initially searched on 18th May 2023 and updated on 20th August 2024 using pre-determined search strategies and included MEDLINE, MEDLINE-In Process, EMBASE, EconLit, and the HTA database, the National Health Service Economic Evaluation Database (NHS EED), and Database of Abstracts of Reviews of Effects (DARE). Hand searches of the grey literature including registries and conference proceedings were performed to identify data not captured in the database searches.

Full details of the search strategies, inclusion and exclusion criteria, and the PRISMA flow diagram are presented in Appendix G.

The initial SLR identified 35 publications of which 28 reported findings from 25 studies and 7 were HTA submissions. Overall, 12 publications describing 10 studies were model-based economic evaluations, and 16 publications describing 15 studies were observational and costing studies.[81] A further 6 publications (2 economic evaluations and 4 observational and costing studies) and no new HTAs were identified during the SLR update. Three of the included studies were conducted in the UK. These were a publication,[82] a HTA submission to NICE[16] and a HTA submission to SMC,[81] all assessing durvalumab in the PACIFIC indication.

No published economic studies were found that assessed the cost-effectiveness of treatments specifically in patients with locally advanced, unresectable, EGFRm NSCLC whose disease did not progress during or following platinum-based doublet CRT. This finding reflects the lack of treatment options available to this specific patient population and disease stage.

Due to the narrow scope of the SLR and the limited identified UK-specific evidence,[16, 81, 82] an additional search of HTA submissions to NICE was conducted in other relevant indications. The search was focused on (1) advanced EGFRm NSCLC appraisals, (2) appraisals modelling therapy after platinum-based CRT in the oncology setting i.e. tumour agnostic (reviewing the approach to cure modelling depending on data maturity) (3) and other relevant osimertinib submissions (TA761[3] and TA654[1]). This search identified 6 additional HTAs.

B.3.1.2 Description of identified studies

An overview of the cost-effectiveness models identified in the 7 relevant HTA submissions to NICE as well as the preferred model structure and comments from the EAG is presented in Table 27.

Table 27: Review of HTA submissions in NSCLC

TA, year	Indication	Intervention	Data maturity	Model structure selected	EAG (formally ERG) comment
TA798[16] (PACIFIC)	Unresectable NSCLC after platinum-based chemoradiation	Durvalumab	Model was initially submitted with 2-year data and then updated with 5-year data at the CDF exit appraisal. OS data was immature in the initial submission, but the 5-year data submitted in the CDF exit appraisal was mature.	State transition model (PF, PD, and death)	In the original appraisal, the ERG raised concern about the post-progression survival estimates as they were based on a small sample of patients who had progressed early in the PACIFIC trial, that may not be representative of all progressors. The ERG requested the manufacturer to submit a PSM to assess any potential bias, but manufacturer responded that all standard parametric curves for PFS and OS crossed, so the PSM model was not submitted. Ultimately, the ERG considered the STM acceptable for decision making.
TA761[3] (ADAURA)	EGFR mutation-positive NSCLC after complete tumour resection	Osimertinib	Immature OS data	State transition model (DF, LRR, DM1, DM2, and death)	The model structure was considered appropriate
TA192[83] (IPASS)	1L locally advanced or metastatic NSCLC	Gefitinib	OS: 37%	State transition model (TrR, stable disease, PD, and death)	OS modelling was an area of concern for the ERG; however they accepted the assumption of a Weibull distribution to extrapolate data beyond the trial.
TA258[84] (EURTAC, OPTIMAL)	1L locally advanced or metastatic EGFR-TK mutation positive NSCLC	Erlotinib	Immature OS data	State transition model (PF, PD, and death)	The ERG highlighted the lack of data to support an OS benefit for erlotinib vs gefitinib and recommended an analysis that assumed equal clinical benefit between treatments.
TA310[85] (LUX-lung 3)	EGFRm positive locally advanced or metastatic NSCLC	Afatinib	Immature OS data	PSM (PF, PD, and death)	The committee criticised the assumption of proportional hazards and the extrapolation of PFS. Specific commentary on the model structure was not provided and assumed appropriate.
TA595[86]	Untreated EGFRm positive locally	Dacomitinib	Mature OS data	PSM (PF, PD, and death)	The committee was concerned that the model captured only the costs and not the clinical benefits of subsequent treatments. However, the committee

TA, year	Indication	Intervention	Data maturity	Model structure selected	EAG (formally ERG) comment
(ARCHER 1050)	advanced or metastatic NSCLC				concluded that the model was generally appropriate and consistent with the models used in other appraisals for NSCLC.
TA654[1] (FLAURA)	Untreated EGFRm positive locally advanced or metastatic NSCLC	Osimertinib	PFS: 61.5% OS: 25%	PSM (PF, PD, and death)	The committee highlighted the limitations of modelling the duration of treatment effect with a PSM, because a crude approach was needed to make adjustments around the assumptions (for example, assuming equivalence at a single time point). The ERG commented that the benefits of subsequent treatments were not captured appropriately. The ERG highlighted the uncertainty in OS estimates, based on data with a 25% maturity, although they accepted the conservative choice of distribution made by the manufacturer.

Abbreviations: CDF, Cancer Drugs Fund; DF, disease free; DM, distant metastasis; EGFRm, epidermal growth factor receptor mutation; ERG, Evidence Review Group; LRR, locoregional recurrence; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PSM, partitioned survival model; STM, state transition model.

B.3.2 Economic analysis

As summarised in Table 27 and discussed in section B.3.1.2, none of the identified economic evaluations compared osimertinib with BSC in locally advanced, unresectable, EGFRm NSCLC, following CRT. Therefore, for the purposes of this submission, a *de novo* economic model was deemed necessary and developed, utilising a semi-Markov model structure with three health states (progression-free, progressed disease and dead).

The analysis was performed from the perspective of the UK NHS and Personal Social Services (PSS), in line with the NICE reference case.[87] Summary characteristics of the economic analysis are presented in Table 28.

Table 28: Summary characteristics of the economic analysis

Aspect	Details	Justification
Model structure	A semi-Markov state transition model, with 3 health states: progression-free (PF), progressed disease (PD) and death. The model utilises tunnel states to track time spent in every health state.	The methodology follows the guidance from (ISPOR and NICE and previous appraisals in NSCLC including TA761).[3] This approach is preferred due to the low maturity of the osimertinib OS data and is discussed in Section B.3.2.2.1.
Patient population	Adults (≥18 years of age) with locally advanced, unresectable EGFRm NSCLC whose disease has not progressed during or following definitive platinum-based CRT.	Aligned with anticipated licensed indication for osimertinib, the LAURA trial population and NICE scope
Intervention	Osimertinib 80 mg once daily (oral administration)	As per NICE scope
Comparator	Placebo (as a proxy for best supportive care, which consists of active monitoring only)	Best supportive care is the only relevant comparator. Durvalumab should not be considered for EGFRm patients, due to the unclear efficacy and the potential increased risk of toxicity as recommended in ESMO expert consensus statements,[32] and as described in section B.1.1
Perspective	UK NHS and PSS	In line with the NICE reference case[87]
Time horizon	Lifetime (38.60 years)	To reflect survival of the patient population: 100 years minus mean starting age (61.40 years)

Aspect	Details	Justification
Cycle length	30 days	To align with the osimertinib treatment schedule, and previous models in the advanced NSCLC setting (Table 27)
Half-cycle correction	Applied in the base case	To adjust for timing of state transitions throughout the cycle.
Discounting	3.5% for costs and benefits	In line with the NICE reference case[87]
Source of utilities	EQ-5D-5L (mapped to 3L UK value set) data collected in LAURA trial for the PF health state. EQ-5D-5L (mapped to 3L UK value set) from the FLAURA trial in the PD state. Please refer to Section B.3.4	In line with the NICE reference case[87]
Source of costs	NHS reference costs, BNF, Unit Costs of Health and Social Care (PSSRU)	In line with the NICE reference case[87]

Abbreviations: BNF, British National Formulary; CRT, chemoradiotherapy; EGFRm, epidermal growth factor receptor mutation; ISPOR, The Professional Society for Health Economics and Outcomes Research; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PSSRU, Personal Social Services Research Unit.

B.3.2.1 Patient population

The target population was aligned with the LAURA trial;[10] patients of ≥18 years of age with locally advanced, unresectable EGFRm NSCLC whose disease has not progressed during or following definitive platinum-based CRT (see Appendix C).

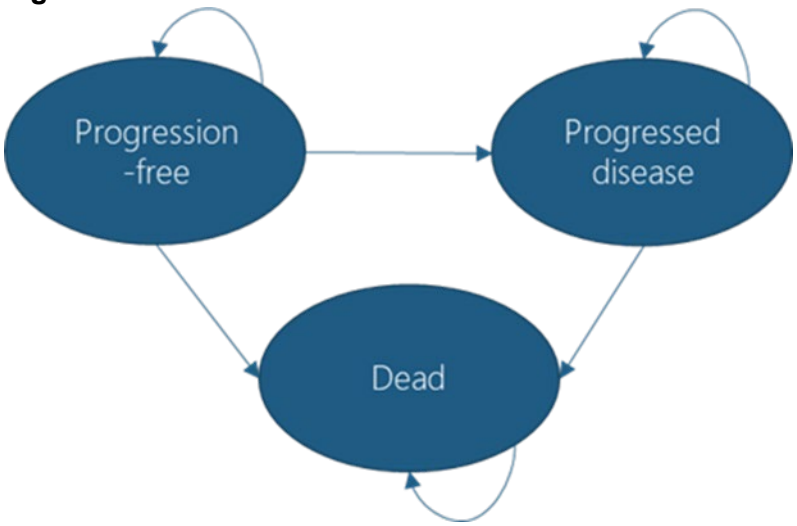
A summary of patient characteristics for the LAURA trial population is shown in Table 7. Demographic and baseline disease characteristics, including the prevalence of EGFR mutation types, stratification factors and clinical staging were generally well balanced between treatment arms, except for WHO performance status (PS) where a lower proportion of patients with a WHO PS of 1 were randomised to the osimertinib arm (44.1%) compared with the placebo arm (57.5%). This difference was not considered to have an impact on the evaluation of efficacy and safety and in the individual treatment arms (see Section B.2.7).

B.3.2.2 Model structure

A *de novo* semi-Markov model was developed in Microsoft Excel®, comprising three health states that represent the disease course and survival of patients over time,

including ‘Progression-free (PF)’, ‘Progressed disease (PD)’ and ‘Death’ as the absorbing health state (Figure 17).

Figure 17: Model structure



All patients enter the model in the PF health state and receive either osimertinib or placebo (as a proxy for BSC). The patient journey through the model is described in Table 29. Whilst in the PF state, patients can remain in PF or transition to either the PD or Dead health state in each cycle. The probability of patients transitioning to the PD state is derived directly from the TTP data collected in the LAURA trial. Those, who experience a fatal event in the PF state, transition to the Dead state according to the difference between PFS and TTP from the LAURA trial, capped by general population all-cause mortality. Following progression, patients may remain in the PD health state or transition to the Dead state, based on PPS data from LAURA and general population all-cause mortality. The Dead state is an all-absorbing state.

Table 29: Transitions between health states (use of LAURA trial data)

Transition	Trial Endpoint	Number at risk		Number of events		Description
		Osi	PBO	Osi	PBO	
TP1: PF to PD	TTP (BICR)	143	73	53	62	TTP is defined as the time from randomization to tumour progression per BICR (deaths without progression are censored). Parametric curves were fitted to the TTP data and extrapolated over a lifetime horizon in order to calculate TP1.
TP2: PF to Dead	PFS-TTP	-	-	-	-	The transition from PF to dead was calculated as the difference between the probabilities derived from the PFS and TTP curves and capped to ensure the risk of mortality is never less than age and sex-matched general population mortality.

Transition	Trial Endpoint	Number at risk		Number of events		Description
		Osi	PBO	Osi	PBO	
						Parametric curves were fitted to the PFS and TTP data and extrapolated over a lifetime horizon in order to calculate TP2.
TP3: PD to Dead	PPS	53	62	24	13	PPS is defined as the time from BICR-confirmed tumour progression according to RECIST until the date of death. (i.e date of death or censoring – date of tumour progression + 1). Only patients who have progressed are included in this analysis population PPS was extrapolated by fitting a parametric curve to PPS Kaplan-Meier data from the clinical trial. This curve then was used to calculate TP3.

Abbreviations: BICR, blinded independent central review; PBO, placebo; PD, progressed disease; PF, progression free; PFS, progression-free survival; PPS, post-progression survival; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

B.3.2.2.1 Rationale for model structure selection

Based on the review of identified previous NICE HTAs (Table 27), both STMs and PSMs have been utilised to assess the cost-effectiveness of treatments for NSCLC. Nevertheless, the majority of these HTA appraisals (4 out of 7) incorporated a STM structure. One (TA798) was specifically for a NSCLC treatment in the post-CRT setting.[16] Additionally, of the five models submitted in advanced EGFRm NSCLC, two (TA761 and TA258)[3, 84] used a STM citing the low maturity of OS data as the rationale. Given the low OS data maturity in the LAURA trial (19.9%) and the positioning of osimertinib treatment following CRT, insights from these three HTAs were of particular interest.

An STM structure allows for the OS endpoint to be extrapolated as a function of PFS and PPS, introducing a structural link between mortality and earlier non-fatal events. Furthermore, an STM structure ensures consistency in the long-term model predictions and avoids logical inconsistencies (i.e. PFS and OS crossing), which are common when low maturity data are extrapolated independently in a PSM approach.

During an advisory board with clinical experts specialising in the treatment of NSCLC, the STM structure was agreed as appropriate and the consensus was that due to the low maturity of data, a PSM approach was less appropriate.[15]

The STM structure has previously been accepted as appropriate for decision-making by NICE specifically in the locally advanced unresectable NSCLC disease setting, following CRT,[16] and in other early lung cancer appraisals.[3]

Given the low OS maturity in the LAURA trial, previously accepted model structures in NICE appraisals in the early lung setting, and the consensus from external experts in an advisory board, a STM structure was considered most appropriate to model long-term survival and robustly capture the costs and benefits of osimertinib in comparison with placebo in this indication.

B.3.2.2.2 General model settings

The model used a cycle length of 30 days to align with recurrent costs and timing of treatment (i.e. daily administration of osimertinib available in a pack size of 30 tablets per pack). This was considered sufficiently granular to capture events occurring during disease progression and was aligned with previous models in the advanced NSCLC setting as described in Table 26.

The starting age (61.4 years) and sex distribution (62.9% female) at model entry reflected the baseline characteristics of patients in the LAURA trial (see Table 7).

A lifetime horizon was applied in the base case analysis (38.6 years, i.e. 100 years minus the starting age of 61.4 years), representing the maximum possible survival for any patient in this modelled population.

A half-cycle correction was applied to adjust for the timing of state transitions throughout each cycle. Half-cycle correction was not implemented to calculate one-off costs (e.g., subsequent treatment, adverse events, and end-of-life costs) and the costs of osimertinib. The costs of osimertinib were modelled on the proportion of patients on treatment at the start of each model cycle.

Costs and quality-adjusted life-years (QALYs) were discounted at a rate of 3.5% per annum, as recommended in the NICE reference case (2022).[87] An alternative discount rate of 1.5% was investigated in a scenario as per NICE guidelines[87] and a rate of 6% was also explored as previously used by NICE.[88]

B.3.2.3 Intervention technology and comparators

The economic model compares the cost-effectiveness of osimertinib with placebo (as a proxy for BSC, which consists of active monitoring only) in line with the intervention and comparators in the LAURA trial. As discussed in Section B.1.1, durvalumab is not considered a relevant comparator due to the uncertain benefit in EGFRm patients and the potential increased risk of toxicity, as advised in the ESMO expert consensus statements, and supported by UK clinicians interviewed.[32]

Osimertinib is expected to be the first licensed treatment for locally advanced, unresectable EGFRm NSCLC patients whose disease has not progressed after platinum-based CRT, representing a substantial innovation in this treatment setting. It is administered orally at a dose of 80 mg once daily.

Best supportive care (i.e active monitoring) represents current UK clinical practice without osimertinib. Active monitoring costs and resource use are captured within the economic model and were validated with UK clinicians as being representative of clinical practice.

Further information on the costs and resource use associated with osimertinib, placebo and subsequent therapies in this analysis is provided in Section B.3.5.2.

B.3.3 Clinical parameters and variables

B.3.3.1 Incorporation of the clinical data into the model

As described in Table 28, the primary data source used to populate the clinical elements of the cost-effectiveness model was the LAURA Phase III trial.[10]

The LAURA Phase III trial, which evaluates osimertinib versus placebo (BSC) in EGFRm patients with locally advanced unresectable NSCLC who have not progressed after CRT, provided efficacy, time to treatment discontinuation, safety, and HRQoL inputs for the semi-Markov model. Specifically, PFS, PPS and TTP data were extrapolated using parametric models and used to derive transition probabilities between the model health states (Section B.3.3.2.3,Table 30). Extrapolated TTD data were used to incorporate osimertinib treatment costs in the model in the PF health state.

Table 30: Overview of clinical data to inform the model

Component	Details	Source
Clinical effectiveness: TTP, PPS and PFS	Transition probabilities between the three health states in the model were derived using TTP, PPS and PFS as follows: • TP1: PF to PD - Derived using the independently extrapolated TTP KM curve for osimertinib and placebo • TP2: PF to dead - Derived using the difference between the probabilities derived from the PFS and TTP curves for osimertinib and placebo • TP3: PD to dead - Derived using the independently extrapolated PPS KM curve for osimertinib and placebo	LAURA trial; FAS; 5th January 2024 data cut[10]
Clinical effectiveness: TTD	Used to model treatment duration for osimertinib with the assumption that the TTD survival curve from the LAURA trial was the best approximate duration of the osimertinib treatment arm (see Appendix M)	LAURA trial, FAS; 5th January 2024 data cut[10]
Adverse event incidence	Informed the proportion of patients who incur costs and utility decrements associated with each AE.	LAURA trial; FAS; 5th January 2024 data cut[10]
Health-related quality of life	PF state: Health-state specific values, derived from the LAURA trial-collected EQ-5D-5L data mapped to the 3L setting using the Hernandez Alava mapping algorithm. PD state: Published literature (TA621)[1] Utility decrements associated with adverse events applied as a one-off at the start of index treatment.	LAURA trial, FAS; 5th January 2024[10] Published literature for PD state utility and AE utility decrements

Abbreviations: AE, adverse event; BICR, blinded independent central review; FAS, full analysis set; KM, Kaplan-Meier; PBO, placebo; PD, progressed disease; PF, progression free; PFS, pre-progression survival; PPS, post-progression survival; TTP, time to progression; TTD, time to discontinuation.

B.3.3.1.1 Parametric extrapolation

Parametric survival modelling was needed to estimate efficacy endpoints for osimertinib and placebo beyond the LAURA trial follow-up period. In accordance with standard practice and guidance from the NICE decision support unit (DSU),[89] seven parametric extrapolation functions (exponential, gamma, generalised gamma, Gompertz, loglogistic, lognormal) were fitted to the LAURA Phase III trial data using a frequentist approach in order to extrapolate relevant endpoints (TTP, PPS,PFS and TTD) prior to inclusion in the model. To assess “goodness of fit” of parametric models, the following criterion were considered:

- **Assessment of the proportional hazards assumption** (PHA) via visual inspection of log-cumulative hazard plots and the Schoenfeld residual test to determine the suitability of using independent models fitted to each arm or joint models that are fitted to a data set containing both arms with a covariate for treatment group.
- **Review of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)** for statistical fit of modelled data compared to observed data. Lower AIC and BIC values demonstrate a better statistical fit of the survival curve
- **Visual inspection of curves for goodness of fit of modelled data compared to observed data (modelled vs KM curves):** Visual inspection was performed by plotting the KM survival curves and comparing them to the extrapolated parametric modelled curves. The curves that appear to best match the KM curves achieve the best-fit criteria.
- **Clinical validity:** Consideration of clinical plausibility of long-term projections based on UK clinical expert opinion.

B.3.3.2 Derivation of transition probabilities between health states

B.3.3.2.1 Transition probability 1: Progression-free to progressed disease

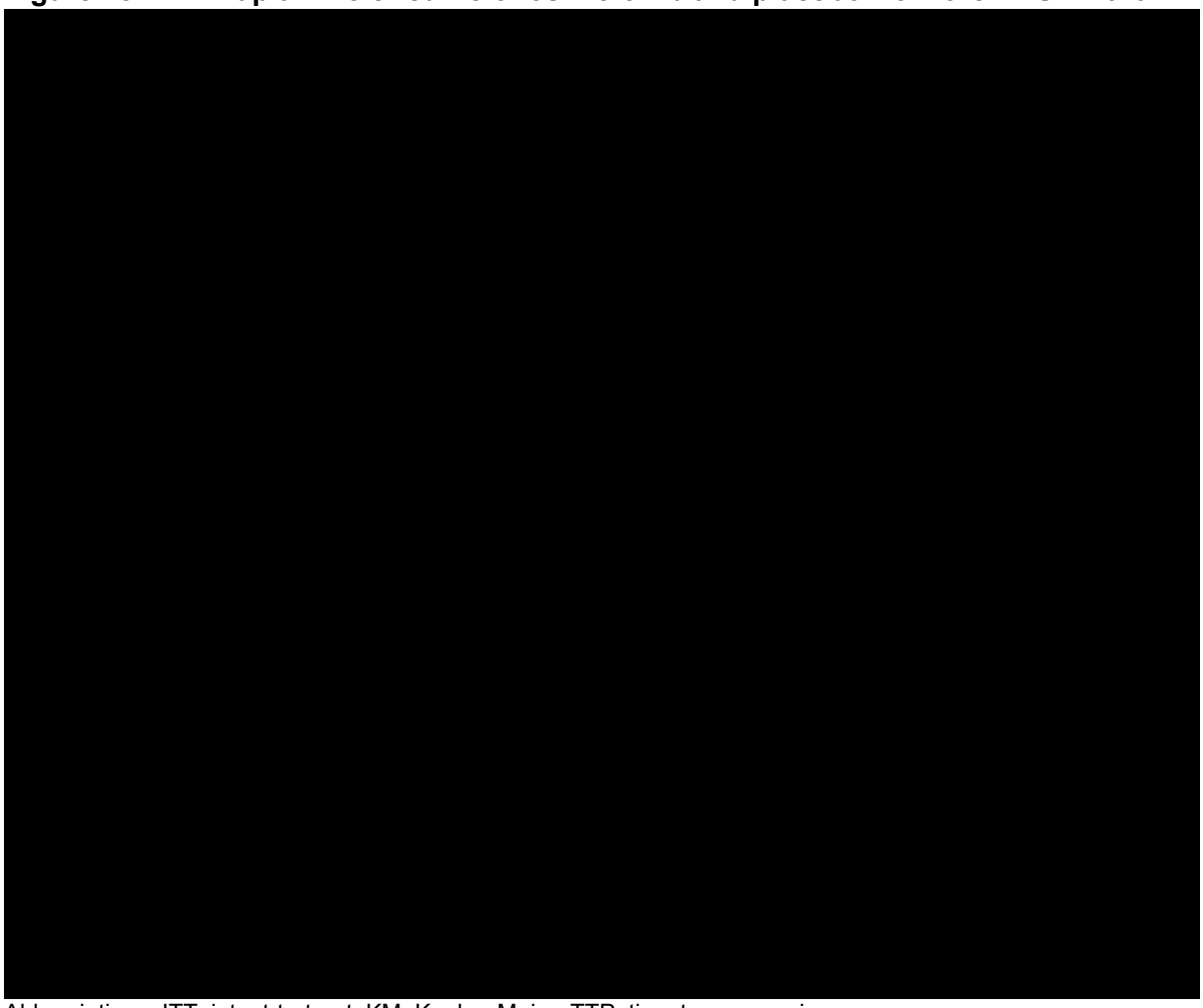
B.3.3.2.1.1 Time to progression trial data and smoothened hazard plots

TTP is defined as the time from randomisation to tumour progression explicitly (deaths without progression are censored observations rather than counted as events). The TTP KM curve is shown in Figure 18.

Of the 143 patients in the osimertinib arm, 53 patients had a BICR confirmed disease progression event (37.1% maturity) at the 05 January 2024 DCO. Median TTP was 39.3 months (95% CI: 38.4, NR), which was consistent with median PFS (39.1 months [95% CI: 31.5, NC]).

Additionally, of the 73 patients in the placebo arm, 62 patients had BICR confirmed disease progression event (84.9% maturity) at the 05 January 2024 DCO. Median TTP was 5.6 months (95% CI: 3.7, 7.4), which was consistent with median PFS (5.6 months [95% CI: 31.7, 7.4]).

Figure 18: TTP Kaplan-Meier curve of osimertinib and placebo from the LAURA trial



Abbreviations: ITT, intent-to-treat; KM, Kaplan-Meier; TTP, time to progression.

As shown in Figure 19, the hazard profile from randomisation up to 28 months for the osimertinib arm was reasonably flat, after which the smoothed hazards started to increase. However, some caution should be applied when interpreting the tail of the hazard function, as the number of patients remaining at risk is low and this causes fluctuations in the hazard function when events occur. The smoothed hazard plot for the placebo arm demonstrated increasing risk of a progression event for the first 6 months, followed by a decline in hazards from 6 to 18 months. This reflects the trends in the placebo KM curve and median TTP, which demonstrated that approximately 50% of patients had a progression event in the first 6 months from randomisation.

Figure 19: Smoothed hazards of TPP for osimertinib and placebo from the LAURA trial

Abbreviations: BICR, blinded independent central review; ITT, intent-to-treat; KM, TTP, time to progression.

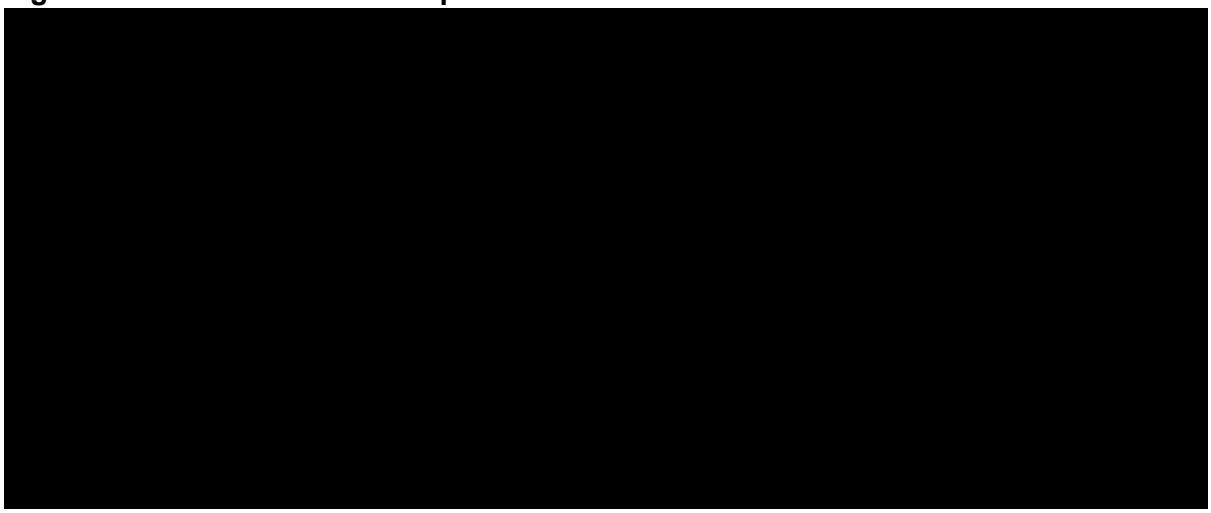
B.3.3.2.1.2 Assessment of proportional hazards assumption

The log-cumulative hazard plot and plot of Schoenfeld residuals for TTP are shown in Figure 20 and Figure 21. The log-cumulative hazards plot showed minor departures from PH with the trend lines in the log-cumulative hazards plot slightly diverging and becoming non-parallel. The Schoenfeld plot showed some evidence of non-proportional hazards, (i.e., a non-horizontal line), but the global test result was not statistically significant (p= 0.9564). On balance it was concluded that the treatment effect for osimertinib may vary over time, and independent models were fit to the KM curves for each arm.

Figure 20: Log curves of TTP

Abbreviations: TTP, time to progression.

Figure 21: Schoenfeld residual plot of TTP



Abbreviations: TTP, time to progression.

B.3.3.2.1.3 Extrapolation of TTP outcomes for osimertinib and placebo

Following NICE DSU TSD 21 guidance[90], it was not considered appropriate to explore more flexible models in this instance, as these models can be unduly influenced by the low patient numbers and may overfit the data (Figure 18). Table 31 and Table 32 present the AIC and BIC statistics for each of the parametric models as well as the observed and modelled median and landmark TTP outcomes for osimertinib and placebo respectively.

Table 31 demonstrates that the log-normal and generalised gamma distributions are associated with the lowest AIC and BIC scores to model the TTP for osimertinib, however, it should be noted that AIC and BIC scores were relatively consistent across all distributions. The AIC scores were within a maximum of 8 points of each other and the BIC scores were within 6 points. With the exception of the generalised gamma and Gompertz distributions, the median TTP of the majority of the distributions were aligned with the median TTP reported by the trial. The landmark survival proportions for the majority of distributions were aligned with the trial TTP up to 3 years. A low number of patients remain at risk from this time point (Section B.2.6.1.1.1).

Table 32 demonstrates that generalised gamma, log-normal and log-logistic curves provided the best statistical fit for the placebo (BSC) arm with very similar AIC and BIC scores (within 5 points of each other); the generalised gamma had the lowest AIC score. At 3 years, the landmark survival results (log-normal: 3.77%; log-logistic: 3.90%; general gamma: 8.73%; KM: 10.97%) show underestimation of the log-normal and log-logistic curves and alignment of the observed KM data with generalised gamma curve which more closely followed the plateau at the end of the curve. However, the plausibility of the long-term plateau for patients receiving placebo is an important point of consideration when selecting the most appropriate parametric model.

Table 31: Observed and estimated TTP rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen-gamma	Gamma	KM curve
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen-gamma	Gamma	KM curve
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; TTP, time to progression.

Table 32: Observed and estimated TTP rates and AIC/BIC of survival models for placebo

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen-gamma	Gamma	KM curve
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; TTP, time to progression.

The extrapolated TTP curves were plotted together with the KM data for osimertinib and placebo from the LAURA trial using standard parametric functions (Figure 22 and Figure 23).

Figure 22 demonstrates a wide variation in the long-term estimates of TTP for the osimertinib arm, which is considered to be driven by the relatively low maturity of the data (37.1%). Furthermore, there are a low number of patients remaining at risk after the 36-month timepoint in LAURA (see Figure 5). The generalised gamma and Gompertz curves, which were two of the best fitted models based on statistical fit, provided the most optimistic estimates of long-term TTP. The exponential provided the most conservative estimate of long term TTP. Of the remaining extrapolations,

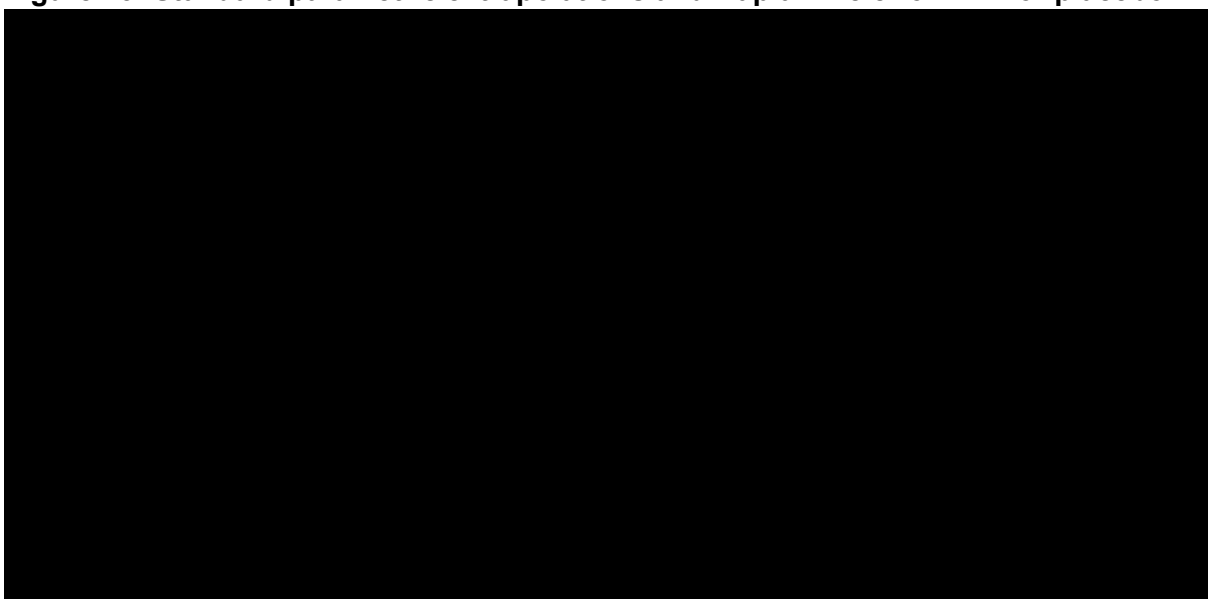
the Weibull and Gamma provided similar estimates, which were more conservative than those from the log-logistic and log-normal.

In contrast, Figure 23 demonstrates little variation in the long-term estimates of TTP for the placebo arm due to the relatively high maturity of the data; 84.9% maturity with 13.71% patients without a progression event at 24 months. The generalised gamma curve provides the most optimistic estimates, which show a small proportion of patients may achieve long-term progression-free survival. Conversely, the log-normal curve estimates all (>99.9%) patients will have had a disease progression event by 77 months.

Figure 22: Standard parametric extrapolations and Kaplan-Meier of TTP for osimertinib

Abbreviations: KM, Kaplan-Meier; TTP, time to progression.

Figure 23: Standard parametric extrapolations and Kaplan-Meier of TTP for placebo



Abbreviations: KM, Kaplan-Meier; TTP, time to progression.

Figure 23 presents the combined smoothed hazard plots for all extrapolations of the osimertinib and placebo arms. All distributions reflect the flat hazards in the osimertinib arm. In the placebo arm, loglogistic, log-normal and generalised gamma all captured the increase followed by decrease in hazards.

Figure 24: Predicted hazards of progression with osimertinib and placebo

B.3.3.2.1.4 Clinician validation

During one-to-one interviews with UK clinical experts with experience in treating NSCLC in November 2024,[15] four out of five clinicians considered the Weibull curve the most clinically plausible extrapolation of TTP in the osimertinib arm. One clinician preferred the more optimistic log-normal curve, which was also considered as a plausible alternative by another clinician.

For the placebo arm, three of the clinicians agreed that the generalised gamma was the most clinically plausible and considered the log-logistic too pessimistic. Nevertheless, the remaining two clinicians considered the log logistic as the most clinically plausible extrapolation.

B.3.3.2.1.5 Summary of base case selection for TTP

For the osimertinib arm, the log-normal and generalised gamma distributions provided the best statistical fit based on AIC/BIC scores but appeared overly optimistic from clinicians' perspectives. Similarly, the Gompertz distribution was a relatively good statistical fit but projected an optimistic long-term outcome that may not be clinically justifiable in this setting. Of the remaining curves, the exponential curve predicted the median TTP consistently with the KM but projected the most conservative long-term outcomes. The remaining log-logistic, gamma and Weibull curves all had a similar statistical fit and were all within 5 points of each other on AIC and BIC. The Weibull was the midpoint between gamma and the log logistic in terms of long-term survival projection. All provided a relatively good fit on the hazard plot, but the Weibull was preferred by four out of five of the consulted UK clinical experts during one-to-one interviews.[15] On balance, the Weibull curve was selected for the base case as it provided a reasonable statistical fit, was visually a reasonable fit for the KM data while providing a more clinically plausible long-term outcome and also provided a good visual fit on the hazard plot. It was also considered one of the more conservative options (Figure 22). The log-normal and gamma distributions were tested in scenario analyses.

For the placebo arm, the generalised gamma and log-normal distributions had the best statistical fit based on AIC and BIC scores. In terms of visual fit to the KM data, all options except the Gompertz and generalised gamma underestimated the

observed data at the tail end of the KM curve. The generalised gamma and log-logistic distributions provided the best visual fit to the hazard plots. The generalised gamma was the preferred approach by three out of five UK clinical experts consulted during one-to-one interviews.[15] On balance, the generalised gamma was selected for the base case as it was deemed a good fit across all three assessments. The log-logistic was tested in a scenario analysis.

B.3.3.2.2 Transition probability 2: Progression-free to death

The PFS endpoint in LAURA was defined as the time from randomisation until the date of objective radiological disease progression according to RECIST or death (by any cause with absence of progression). A patient who had not progressed or died at the time of analysis, or who progressed or died after two or more missed visits was censored at the time of the latest evaluable visit.

As such, the PFS curve captures both progressed disease and death, whereas TTP only captures progressed disease as discussed in Section B.3.3.2.1.1 The differences between the PFS and TTP curves inform the transition probability from the PF health state to dead. The changing slope of the PFS and TTP curves over time reflected the changing hazards, indicating that TP1 and TP2 were dependent of the time spent in the PFS health state.

$$TP_2 = 1 - \frac{S^{PFS}(t)}{S^{PFS}(t-u)} - TP_1$$

$where$ TP, transition probability; S, predicted survival at time t; t, time; u, cycle length

In the model, for each cycle the probability of patients who progress only from the previous cycle was calculated from TTP (TP1). The probability of patients who progress or die (TP1+TP2) was calculated from PFS. The respective cycle's probability of transitioning from PF to dead (TP2) is calculated as the difference between these probabilities.

These transition probabilities were adjusted for general population mortality to ensure external validity where mortality in the model is never lower than the general population mortality.

B.3.3.2.2.1 Extrapolation of PFS outcomes for osimertinib and placebo

The survival distribution for the extrapolation of PFS data in both the osimertinib and placebo arms was aligned with that for TTP, due to TTP being a derivative of PFS and to avoid as much as possible the illogical crossing of PFS and TTP curves. During five one-to-one interviews with UK clinical experts with experience in treating NSCLC in November 2024,[15] all clinicians agreed that the distribution selected for TTP should be aligned with that selected for PFS.

This approach is further supported by evaluation of statistical and visual fit of the same seven parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, gen-gamma and gamma) fitted to the PFS KM data from LAURA for osimertinib and placebo. As indicated in Table 33 and Table 34, the trends in AIC and BIC scores as well as landmark estimates for osimertinib and placebo for PFS are aligned with those for TTP in Table 31 and Table 32, respectively as described in B.3.3.2.1.1 Similarly, as shown in Figure 25 and Figure 26 for osimertinib and placebo, respectively, the trends in visual fit of parametric models for PFS are aligned with those for TTP in Figure 22 and Figure 23. For completeness with other reporting, the diagnostic plots for the assessment of the PHA and the hazard plots for PFS have been provided in Appendix M.

Table 33:Observed and estimated PFS rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen-gamma	Gamma	KM curve
AIC	573.90	573.40	571.50	571.50	567.90	567.00	574.00	-
AIC rank	5	4	3	3	2	1	6	-
BIC	576.90	579.30	577.50	577.40	573.80	575.90	575.90	-
BIC rank	3	4	6	5	1	2	2	-
Median (months)	37.45	40.41	44.35	41.40	42.38	52.24	39.43	39.13
1 year	80.11%	77.58%	75.98%	76.39%	75.71%	73.00%	78.09%	72.95%
2 years	64.74%	64.10%	62.72%	62.93%	62.70%	62.01%	64.40%	65.15%
3 years	52.32%	53.81%	54.50%	53.67%	54.09%	55.76%	53.68%	58.36%
5 years	34.18%	38.90%	45.60%	41.58%	42.89%	48.33%	37.88%	44.79%
10 years	11.55%	18.49%	37.76%	25.68%	27.56%	37.85%	16.28%	-
15 years	3.76%	9.06%	33.10%	17.31%	18.92%	30.49%	7.01%	-

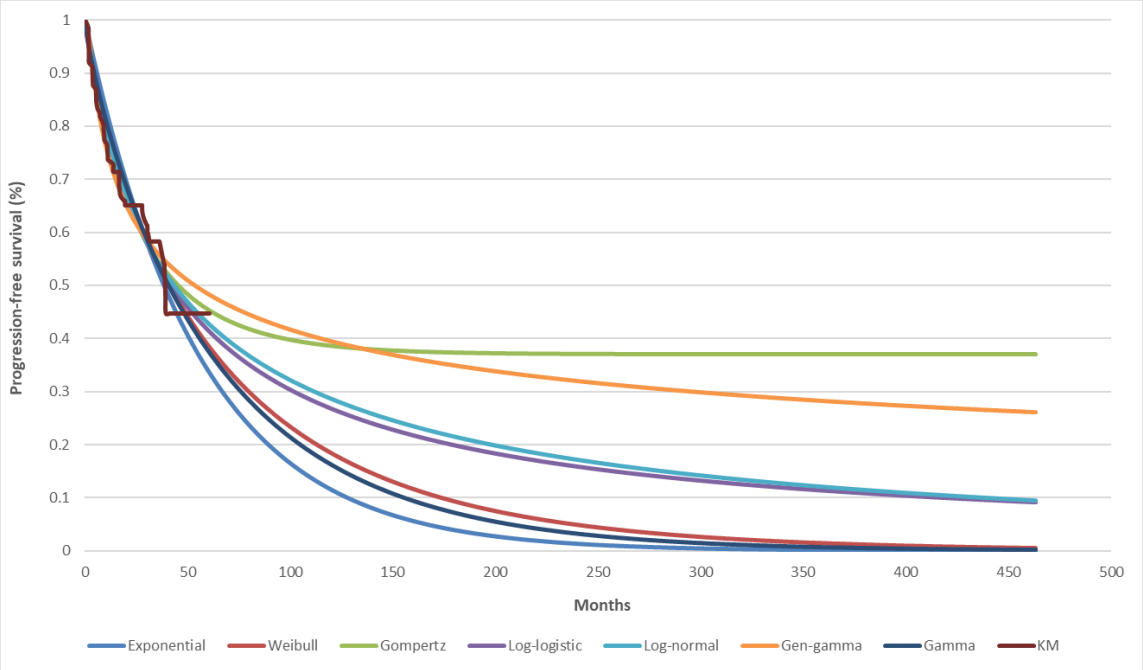
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; PFS, progression-free survival.

Table 34:Observed and estimated PFS rates and AIC/BIC of survival models for placebo

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen-gamma	Gamma	KM curve
AIC	421.00	423.00	417.80	401.60	401.80	393.20	421.40	-
AIC rank	5	7	4	2	3	1	6	-
BIC	423.30	427.50	422.30	406.10	406.40	400.10	426.00	-
BIC rank	5	7	4	2	3	1	6	-
Median (months)	5.91	5.91	4.93	4.93	5.91	4.93	6.90	5.55
1 year	30.03%	30.06%	27.33%	21.15%	24.55%	23.25%	29.68%	21.81%
2 years	9.45%	9.18%	11.89%	7.21%	8.03%	11.86%	7.82%	12.46%
3 years	2.97%	2.77%	6.80%	3.60%	3.39%	7.92%	1.98%	6.6%
5 years	0.29%	0.25%	3.62%	1.44%	0.91%	4.73%	0.12%	-
10 years	0.00%	0.00%	2.27%	0.38%	0.09%	2.25%	0.00%	-
15 years	0.00%	0.00%	1.93%	0.16%	0.02%	1.36%	0.00%	-

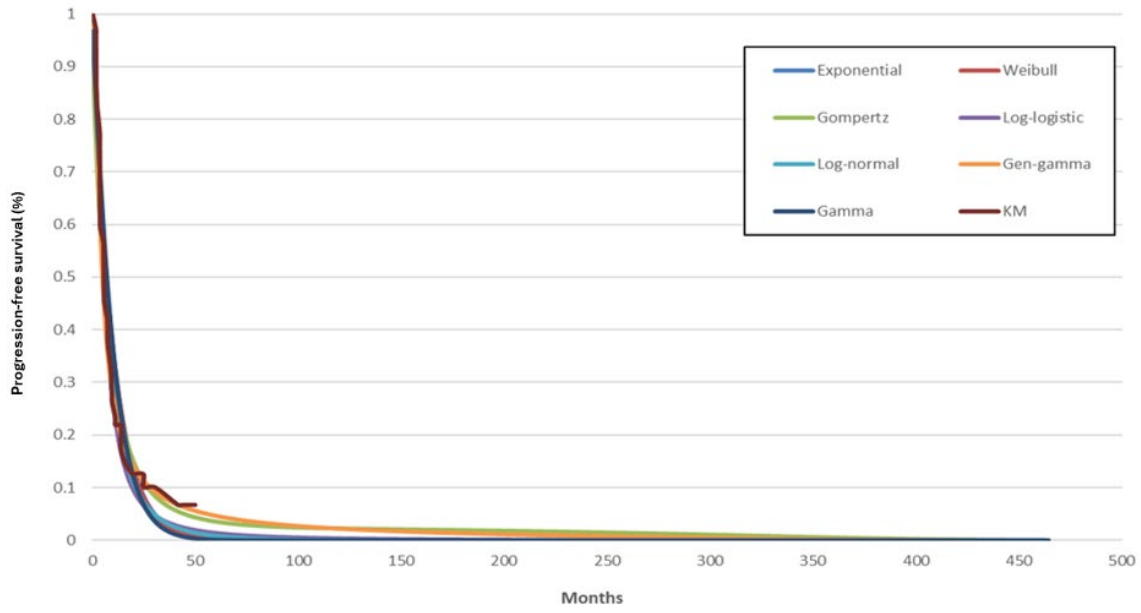
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; PFS, progression-free survival.

Figure 25: Standard parametric extrapolations and Kaplan-Meier of PFS for osimertinib



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 26: Standard parametric extrapolations and Kaplan-Meier of PFS for placebo



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

For both TTP and PFS, the models with best statistical and visual fit in the osimertinib arm were the generalised gamma and log-normal whereas the gamma and exponential had the worst statistical and visual fit and provided the most conservative long-term extrapolations. Similarly, for both placebo TTP and PFS, the generalised gamma had the best statistical fit but only generalised gamma and Gompertz had a good visual fit with all other parametric models underestimating observed KM values.

On balance and aligned with TTP curve selection, the Weibull was considered most appropriate for the extrapolation of the PFS KM data in the osimertinib arm. Similarly, for placebo, the generalised gamma was selected in the base case.

B.3.3.2.3 Transition probability 3: Progressed disease to death

B.3.3.2.3.1 Post-progression trial data and smoothed hazard plots

Transitions from PD to death were estimated from the PPS curve for both osimertinib and placebo. PPS is defined as the time from BICR-confirmed tumour progression according to RECIST until the date of death. (i.e. date of death or censoring – date of tumour progression + 1). Changes in the hazard of the PPS curve over time meant

that this transition probability (TP3) was a function of the time spent in the PD health state but was not dependent on time spent in the PF state.

$$TP3 = 1 - \frac{S^{PPS}(t)}{S^{PPS}(t-u)}$$

$where$ TP, transition probability; S, predicted survival at time t; t, time; u, cycle length

The PPS KM curves for osimertinib and placebo from LAURA trial are shown in Figure 27 and the smoothed hazard plots are shown in Figure 28.

Due to the immaturity in the osimertinib TTP survival curve, the osimertinib PPS curve started with only 53 patients (of the 143 randomised in the trial) at risk. In total, 24 patients of the 53 at risk had a death event (45.3% maturity) at the time of DCO1 (5th January 2024). The median PPS for osimertinib was 32.0 months (95% CI: 18.8, NR). There was a steeper decrease in the KM plot observed from approximately 24 months, however, only 18 patients remained at risk at this timepoint, and hence small event numbers can lead to large visual changes in the KM. The hazard plot was somewhat challenging to interpret due to the low numbers of patients at risk but appeared to demonstrate an initial decline in hazards up to 12 months followed by an increase in hazards, which again should be interpreted with caution due to the low numbers of patients at risk, especially from 24 months.

In total, 62 patients in the placebo arm (of the originally randomised 73) were at risk in the PPS curve and 13 patients had a death event (21.0% maturity) at the time of DCO1. The median PPS for placebo was 41.8 months (95% CI: 32.69, NR). The hazard plot (Figure 28) demonstrated increasing hazards throughout the trial period, with a notable decline at month 33, although this is based on a very small sample size (N<15). The PPS data should also be interpreted in the context of the >80% crossover to osimertinib in the placebo arm. Osimertinib is considered first-line SoC in UK clinical practice for patients with locally advanced or metastatic EGFRm NSCLC, based on the results of the FLAURA trial.[91] Therefore, is it anticipated that the placebo patients will experience improved PPS outcomes compared with patients who have already progressed on osimertinib. This was confirmed by UK clinicians during one-to-one interviews in November 2024,[15] who commented that they expect 80–90% of placebo patients in the progressed disease setting to receive

osimertinib. This was also consistent with the LAURA study, where 80.6% of patients in the placebo arm received osimertinib after confirmed disease progression.[10] With further follow-up, a decline in the PPS curve is expected in the placebo arm as patients experience disease progression while receiving first-line advanced/metastatic treatment.

Figure 27: Post-progression Kaplan-Meier curve of osimertinib and placebo from the LAURA trial

Abbreviations: BICR, blinded independent central review; ITT, intent-to-treat; KM, Kaplan-Meier.

Figure 28: Smoothed hazards of post-progression for osimertinib and placebo from the LAURA trial

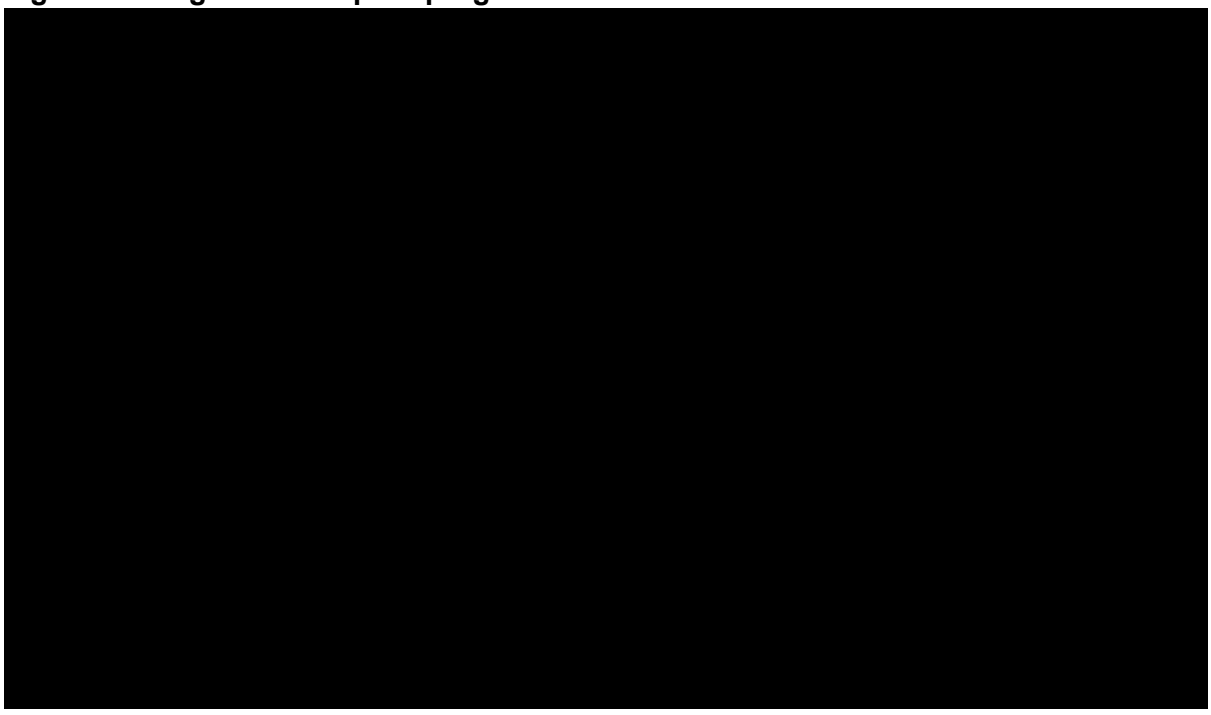
Abbreviations: BICR, blinded independent central review; ITT, intent-to-treat.

B.3.3.2.3.2 Assessment of proportional hazards assumption

The Schoenfeld and log-cumulative hazards plots for PPS are shown in Figure 29 and Figure 30. The unadjusted Schoenfeld test result was p=0.6665. The log-hazard ratio in the Schoenfeld plot showed some evidence of non-proportional hazards, (i.e., a non-horizontal line), however there was no clear pattern or trend in the treatment effect over time. A visual inspection was performed which showed that the test lacked validity. Therefore, the proportional hazards assumption was not considered to hold. These results indicate that the treatment effect for osimertinib may vary over time, and hence independent models were selected for the parametric models.

Figure 29: Schoenfeld residual plot of post-progression survival

Figure 30: Log curves of post-progression survival



B.3.3.2.3.3 Extrapolation of post-progression outcomes for osimertinib and placebo

It was not considered appropriate to explore more flexible models as described in NICE DSU TSD 21[90] as these may be unduly influenced by the low patient numbers informing these curves and may overfit the data. Parametric distributions were fit independently to each arm. Table 35 and Table 36 present the AIC and BIC statistics

for each of the parametric models as well as the observed and modelled median and landmark PPS outcomes for osimertinib and placebo, respectively.

Table 35 shows that the exponential and Gompertz distributions provide the best within-trial fit for the osimertinib arm, as they have the lowest AIC and BIC scores. However, it should be noted that all AIC and BIC scores are relatively consistent. All curves estimate a relatively consistent median PPS (26.61 – 27.60 months), but underpredict compared to the observed data (31.18 months). However, the long-term estimates vary more widely, with projections between 0.0% and14.4% at 10 years.

The exponential and Gompertz distributions also provide the best within-trial fit for the placebo arm, as they have the lowest AIC and BIC scores. Conversely, all the distributions overestimate the median PPS for the placebo arm and the range of estimates for the median and long-term PPS outcomes vary widely.

Table 35: Observed and estimated PPS rates and AIC/BIC of survival models for osimertinib

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen-gamma	Gamma	KM curve
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; PPS, post-progression survival.

Table 36: Observed and estimated PPS rates and AIC/BIC of survival models for placebo

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Gen-gamma	Gamma	KM curve
AIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BIC rank	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan-Meier; PPS, post-progression survival.

The extrapolated PPS curves were plotted together with the KM data for osimertinib and placebo and are provided in Figure 31 and Figure 32. These diagrammatically show the wide variation in long-term PPS outcomes for both arms as described above.

Figure 31: Standard parametric extrapolations and Kaplan-Meier of post-progression for osimertinib

Abbreviations: KM, Kaplan-Meier.

Figure 32: Standard parametric extrapolations and Kaplan-Meier of post-progression for placebo

Abbreviations: KM, Kaplan-Meier.

The predicted hazards plots for osimertinib and placebo are presented in Figure 33. The generalised gamma and Gompertz curves are the only selections which reflect the observed increase in hazards, other parametric models have a much flatter hazard profile. However, the Gompertz distribution more closely aligns with the smoothed hazard profile of both osimertinib and placebo.

Figure 33: Predicted hazards of post-progression survival with osimertinib and placebo

Abbreviations: BICR, blinded independent central review; ITT, intent-to-treat.

B.3.3.2.3.4 Clinician validation

During one-to-one interviews with UK clinical experts in November 2024,[15] three out of five agreed that the Gompertz curve was the most realistic distribution for osimertinib from a UK clinical practice perspective. However, some of these clinicians commented that the decline may be too rapid. The remaining two clinicians considered the lognormal curve could be a reasonable approximation. These same two clinicians also selected a more optimistic extrapolation for the placebo arm (e.g. Weibull).

Three of the clinicians agreed that the Gompertz was also plausible for the placebo arm and noted that all other distributions were quite optimistic. Weibull was also considered plausible by three of the clinicians as it allowed for a tail.

B.3.3.2.3.5 Summary of base case selection for PPS

The Gompertz distribution is selected as the base case for both the osimertinib and the placebo arms. This selection is made based on good statistical fit to the

observed data and good visual fit to the KM data, particularly for the placebo arm. It also appropriately reflects the increasing hazards in both arms. Additionally, it was considered plausible approach by the majority of clinicians during one-to-one interviews. Based on the similar trends in PPS KM curves and smoothed hazards for the osimertinib and placebo arms, as well as clinical input, it is considered most appropriate to select the Gompertz distribution for both arms.

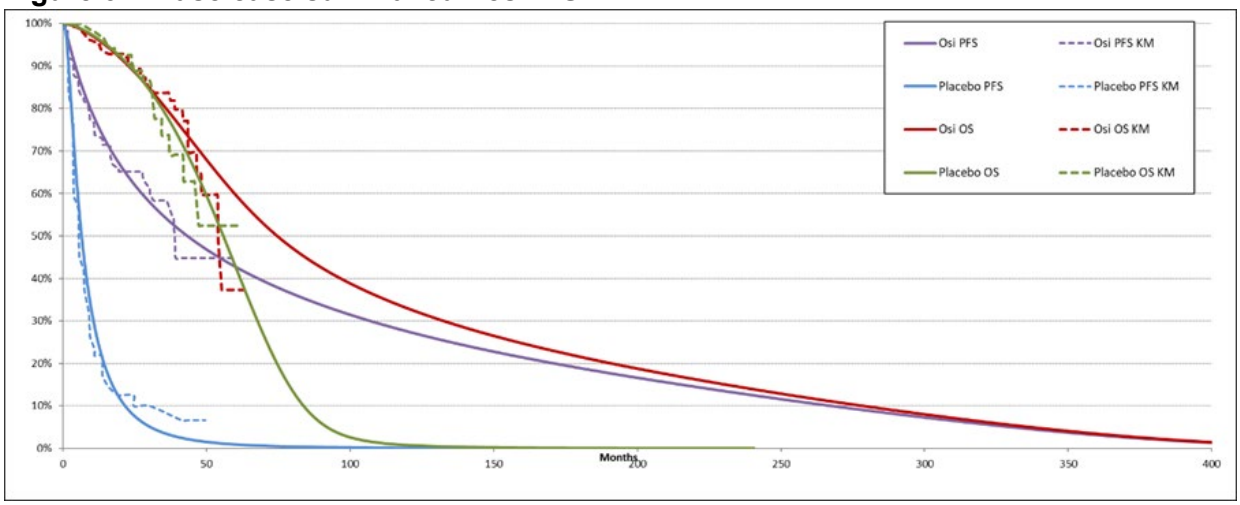
A scenario is explored whereby the more optimistic distributions that were mentioned by the clinicians are tested in both arms concurrently (lognormal for osimertinib and Weibull for placebo).

B.3.3.2.4 Assessment of PFS and aggregated OS curves

In the STM, OS is determined by a combination of survival models (pre-progression death as well as post-progression death). The PFS curve is chosen based on the model selected for TTP. The resulting OS and PFS curves based on the chosen models for PPS and TTP are shown in Figure 34.

The LAURA trial has demonstrated an overwhelming PFS benefit for osimertinib (HR: 0.16 [95% CI: 0.10, 0.24]; p<0.001) and a favourable OS trend (HR=0.81 [95% CI: 0.42, 1.56] p-=0.530) with only 19.9% maturity. While placebo patients appear to experience more optimistic survival outcomes in the PPS setting, which may be interpreted in the context of substantial crossover on progression to osimertinib in the placebo arm, the PFS benefit of osimertinib, i.e. the delayed transition of patients from the PF health state to the PD health state, results in a long term OS benefit from the STM, i.e. when OS is a function of all three transition probabilities in the model. Further validation of the curves was conducted during one-to-one interviews with UK clinicians.[15] This is anticipated to be observed within the trial with longer follow-up. Experts agreed that the LAURA PFS curves and the demonstrated benefit in the osimertinib arm, along with the shape of the curves was as they had expected.

Figure 34: Base case survival curves in STM



Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; STM, state transition model.

B.3.3.3 Extrapolation of time to treatment discontinuation for osimertinib

The TTD KM curve is used directly in the model and extrapolated using the exponential distribution when a low number of patients at risk remains (see Appendix M). This approach was taken in order to best capture the time on treatment within the LAURA trial whilst extrapolating appropriately and in line with clinical expectations.

Osimertinib is a treat-to-progression regimen, however, during an online clinical advisory board with eight clinicians, it was discussed that an indefinite duration of osimertinib treatment is unlikely to occur in practice. Although osimertinib is considered to have a tolerable safety profile, it is not without toxicity, and clinicians referenced expecting 3–5 years of treatment after which patients may be taken off treatment even if progression-free.[15]

To capture this clinical expectation, the observed TTD KM was utilised directly in the model up to month 36, after which an exponential distribution was assumed for the outer years. Furthermore, to reflect the feedback that patients are unlikely to remain on treatment indefinitely, it was assumed that no patients would remain on treatment beyond 10-years. The 10-year TTD cap was removed in a scenario analysis (see B.3.11.3). This increased the ICER slightly to £25,249, which is still below the

acceptable threshold of £30,000. The assumption of a TTD cap was considered to be a pragmatic and aligned with feedback received from clinical experts in the UK. Additionally, a treatment stopping rule for osimertinib of 3 years was applied and accepted in TA761, consistent with the design of the ADAURA trial.[3]

The 36-month timepoint was selected as beyond this timepoint there were very few patients at risk (N<10) in the LAURA trial. This is shown in Figure 35 alongside the base case PFS curve. For completeness, full reporting of the survival analysis performed on the TTD endpoint for the osimertinib arm has been provided in Appendix M.

Figure 35: Osimertinib time to treatment discontinuation

Abbreviations: KM, Kaplan Meier; PFS, progression-free survival; TDT, time to treatment discontinuation.

B.3.3.4 External validation

There is a lack of published RCT evidence on EGFRm patients with locally advanced, unresectable NSCLC following treatment with CRT, with or without further pharmacological therapy which can be used to validate the clinical plausibility of the long-term progression-free and overall survival estimates projected by the economic model. The clinical SLR identified four publications reporting survival outcomes for EGFRm patients; two of these concerned the LAURA trial.[67, 70] Nadioo et al. (2023),[64]),[64] reported PFS and OS outcomes for EGFRm patients from a post hoc analysis of the PACIFIC trial and Ryan et al. (2024)[92] which was a news article

reporting PFS data for aumolertinib from the POLESTAR trial (median OS was not reached).

An additional ad hoc hand search was conducted to identify observational studies conducted in the population of interest as these types of studies were excluded from the clinical SLR. Additionally, AstraZeneca are sponsoring a global RWE study, LEROS,[77] which aims to assess mutation testing, treatment patterns and clinical outcomes in patients with unresectable stage III EGFRm NSCLC. This study has also been included in the list of external validation studies.

Progression-free and overall survival outcomes from relevant sources identified via these searches are presented in Table 37 and Table 38, respectively.

B.3.3.4.1 Progression-free survival

Median PFS in the external studies was slightly higher than the placebo arm of the LAURA trial (5.6 months). Four out of the six studies which reported median PFS measured PFS from the initiation of CRT, and two measure PFS from the completion of CRT. In the LAURA trial, PFS was measured from ran1domisation after patients had completed at least 2 cycles of CRT. It is expected that PFS would be longer in the studies that measured PFS from the initiation of CRT. If accounting for the 2 cycles of CRT, the median PFS in LAURA is broadly aligned to the external studies. Patient numbers should also be considered, which were particularly limited for the EGFRm subgroup of the PACIFIC study. Data on long-term PFS rates were limited and suggested that at 2 years, between approximately 7-30% of patients remain progression free, again noting the limitations in studies reporting PFS from CRT initiation. This is relatively consistent with the PFS rate of 12.5% reported from the LAURA trial for the placebo arm.

B.3.3.4.2 Overall survival

The placebo arm in the LAURA trial did not reach median OS at DCO1 (05 January 2024). However, several sources have been identified via ad hoc hand searching that report a median OS for EGFRm patients post-CRT of 43.0 to 60.9 months (Table 38). Again, data are limited by small patient numbers and measurements from CRT initiation rather than treatment initiation post CRT. The median OS predicted by

the model for the BSC comparator is 52.24 months and therefore is at the more optimistic end of the range identified by literature. One study reported a 2-year OS of 75% for EGFRm patients treated with CRT and observational monitoring, compared with the more optimistic 90.8% 2-year OS rate reported for placebo patients from the LAURA trial. One study reported 5-year OS of 51% (from initiation of CRT), which is also consistent with the model predicted 5-year OS of 40%.

Overall, this suggests both the LAURA trial data and model projections of progression-free and overall survival for the placebo arm may be broadly comparable to data reported in literature and therefore increases certainty in modelled outcomes.

As per the CSR, LAURA is the only RCT to have published outcomes for unresectable, locally advanced EGFRm patients who have received osimertinib post-CRT and therefore, no literature was available to validate outcomes for the osimertinib arm of the trial.

Table 37: Studies reporting progression-free survival

Publication (study)	Study design	Country	Sample	Median age	Population	PFS measure approach	Intervention/ comparator	Median PFS (months)	PFS rates
Naidoo et al. 2023[64] (PACIFIC)	RCT	North America, South America, Europe, Asia, South Africa, Australia	EGFRm subgroup: n=35	67	Unresectable stage III NSCLC with no progression following CRT	From the completion of CRT	Durvalumab (n=24)	11.2 (7.3–20.7)	NR
							Placebo (n=11)	10.9 (1.9–NE)	
Horinouchi et al. 2020[5] (SOLUTION)	Observational, retrospective cohort study	Japan	EGFRm subgroup: n=29	65 (EGFRm subgroup NR)	Unresectable stage III NSCLC with no progression following CRT	From the completion of CRT	NA	16.9	~20% at 3-4 years
Tanaka et al. 2015[72]	Retrospective	Japan	EGFRm subgroup: n=29	62	Inoperable stage III adenocarcinoma patients who received definitive concurrent CRT	From the initiation CRT	NA	9.8 (7.6–19.0)	2yrs[**]: 7.7%
Nassar et al. 2024[93]	Retrospective	United States, Canada, Europe, and Asia	N=136	66	Stage III locally advanced, unresectable EGFRm with no progression following concurrent CRT	From the initiation of CRT	Osimertinib (n=33)	NR (NR-NR)	2yrs: 86% (73-100)
							Durvalumab (n=56)	12.7 (10.5-15.5)	2yrs: 30% (20-45)
							Observation (n=47)	9.7 (6.1-12.0)	2yrs: 27%
Akamatsu et al. 2014[94]	Retrospective	Japan	EGFRm subgroup: n=13	EGFRm subgroup: 68	Unresectable, locally advanced lung adenocarcino	From the initiation of CRT	NA	9.6	NR

Publication (study)	Study design	Country	Sample	Median age	Population	PFS measure approach	Intervention/ comparator	Median PFS (months)	PFS rates
					ma patients treated with concurrent CRT				
Neal et al. 2024[77] (LEROS)	Retrospective	South Korea, US, Japan, UK	N=73	66	Stage III, unresectable, EGFRm NSCLC patients who received CRT alone or CRT with durvalumab	From treatment initiation		9.0 (6.1, 10.4)	6mo: 64% (52, 74) 12mo: 32% (21, 43)

** The 2-year PFS rate was reported as recurrence free survival rate.
Abbreviations: CRT, chemoradiation; EGFRm, epidermal growth factor receptor mutation; NA, not applicable; NE, not evaluable; NR, not recorded; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial.

Table 38: Studies reporting overall survival

Publication (study)	Study design	Country	Sample	Median age	Population	Intervention/ comparator	Median OS (months)	OS rate
Naidoo et al. 2023 (PACIFIC)	RCT	North America, South America, Europe, Asia, South Africa, Australia	EGFRm subgroup: n=35	67	Unresectable stage III NSCLC with no progression following CRT	Durvalumab (n=24)	46.8 (29.9–NE)	NR
						Placebo (n=11)	43.0 (14.9–NE)	
						CRT + no cetuximab	21.1 (17.2-29.2)	
Tanaka et al. 2015[72]	Retrospective	Japan	EGFRm subgroup: n=29	62	Inoperable stage III adenocarcinoma patients who received	NA	51.1 (28.2-70.2)	NR

Publication (study)	Study design	Country	Sample	Median age	Population	Intervention/ comparator	Median OS (months)	OS rate
					definitive concurrent CRT			
Nassar et al. 2024	Retrospective	United States, Canada, Europe, and Asia	N=136	66	Stage III locally advanced, unresectable EGFRm with no progression following concurrent CRT	Osimertinib (n=33)	NR (NR-NR)	2yr: 92% (82-100)
						Durvalumab (n=56)	54 (46-NR)	2yr: 81% (72-93)
						Observation (n=47)	51 (32-71)	2yr: 75% (64-89)
Akamatsu et al. 2014[94]	Retrospective	Japan	EGFRm subgroup: n=13	EGFRm subgroup: 68	Unresectable, locally advanced lung adenocarcinoma patients treated with concurrent CRT	NA	57.9	NR
Neal et al. 2024 (LEROS)[77]	Retrospective	South Korea, US, Japan, UK	N=73	66	Stage III, unresectable, EGFRm NSCLC patients who received CRT alone or CRT with durvalumab	NA	From treatment initiation: 60.9 (44.4, 66.9) From index date: 60.9 (46.9, 66.9)	5yr, from treatment initiation: 51% (38, 62) 5yr from index date: 51% (38, 62)

Abbreviations: CRT, chemoradiation; EGFRm, epidermal growth factor receptor mutation; NA, not applicable; NE, not evaluable; NR, not recorded; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial.

B.3.3.5 General population mortality

Background mortality adjustments was made using general population mortality data. In the base-case analysis, mortality in the PF and PD states was capped using background population mortality in both treatment arms. The hazard of death for patients would not be lower than the hazard of death of the general population (age- and gender-matched). General population mortality data from 2021 was obtained from life tables published by the Office of National Statistics for England and Wales,[95] as per NICE recommendations.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality of life data were collected in the LAURA trial using the European Quality of Life 5-dimension 5 level (EQ-5D-5L) questionnaire. EQ-5D-5L was collected at randomisation and during treatment at week 4, week 8 and every 8 weeks thereafter. EQ-5D-5L data were also collected at treatment discontinuation, and at progression follow-up and survival follow-up. The number of observations collected is presented in Table 39.

Table 39: The number of subjects and observations

Treatment	Scenario	Subjects	Observations
Pooled treatments	Pre-progression	[redacted]	[redacted]
Pooled treatments	Post-progression	[redacted]	[redacted]

B.3.4.2 Mapping

A mixed model for repeated measures (MMRM) analysis was used to estimate HSUVs for the progression-free and progressed disease health states from the collected EQ-5D-5L profiles[96] and subsequently mapping them using the-relevant UK 3L value set and methodology reported in Hernandez-Alava et al. (2023)[97] in accordance with the NICE DSU TSD 22.[98]

An MMRM method was used to account for repeated measurements in the study. This was performed on a dataset excluding observations recorded after the time of censoring for progression, as observations during censoring have an unknown health status.[96]

In total, 4 MMRMs were fitted to the patient-level data. These included models with adjustment for randomised treatment, progression status, an interaction term for randomised treatment and progression status (product of sums) and an interaction term for randomised treatment and progression status (product of multiplication). For input to the economic model, the mean utility (and its associated variance) by treatment arm and/or health state were estimated via least squares (marginal means) from the best fitting models.

According to AIC, the best fitting MMRM was the model that contained a covariate for progression status. The MMRM analysis was therefore performed using the restricted maximum likelihood (REML) method, with progression status, included as a covariate for fixed effects. The marginal ('least square') mean was estimated to provide the mean utility score by progression status that is averaged over observations and with adjustment for repeated measures.

The final HSUVs derived from the LAURA trial data[96] are reported in Table 40

Table 40:Utility values derived from LAURA trial data

	Progression free	SE	Progressed disease	SE
EQ-5D-3L (modelled using MMRM)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MMRM, mixed model for repeated measures; SD, standard deviation.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify HRQoL studies from the published literature relevant to the decision problem. In particular, EQ-5D health state utility values (in line with the NICE reference case) relating to adult patients with locally advanced unresectable, stage III NSCLC, post CRT were sought.

Electronic databases were initially searched on 25th May 2023, and updated on 28th August 2024 using pre-determined search strategies and included MEDLINE, MEDLINE-In Process, EMBASE, the NHS EED, and DARE.

Two publications were included from electronic database and clinical trial register searches. A further 5 HTA reports were identified from hand searches. All identified publications and HTA reports were related to the PACIFIC trial. Detailed methods and results are described in Appendix H.

B.3.4.4 Considerations for alternative utility values in the model PD health state

The HSUV for the post-progression health state from the LAURA trial was associated with uncertainty due to the limited number of observations recorded (n=435) compared with the pre-progression health state (n=2189) as well as low maturity of the data. Observations in the post-progression health state reflecting only HRQoL observed close to the time of progression are not fully reflective of the expected decline in HRQoL as disease progress further and symptoms become more extensive. Therefore, in addition to the trial derived utility values, other sources of utility were considered (see Table 41). These utility values were identified

as part of the systematic review previously described in section B3.4.3 (PACIFIC trial) and the previously conducted hand searches described in Section B.3.1.2, Table 27. A summary of considered values and rationale for inclusion is provided in Table 41.

Table 41: Alternative post-progression HSUVs

HSUV	Source	Rationale for inclusion
0.793	PACIFIC health economic model (post-progression health-stated)[16]	Only model identified evaluating treatments in the same disease stage and treatment setting as LAURA
0.794	FLAURA health economic model (progression-free health state)[1]	Only model identified which evaluates osimertinib for locally advanced and metastatic EGFRm NSCLC
0.640	Labbe et al. 2017 (metastatic EGFRm NSCLC progressing on treatment, used in post-progression health state in the FLAURA model)[99]	Only model identified which evaluates osimertinib for locally advanced and metastatic EGFRm NSCLC and provides a HSUV for the post-progression setting

Abbreviations: EGFRm, EGFR mutations; HSUV, health state utility value; NSCLC, non-small cell lung cancer.

B.3.4.5 Adverse reactions

Adverse events (AEs) were included in this analysis to reflect the health care costs and loss of HRQoL due to toxicities associated with each intervention. All AEs included in the model were treatment-related AEs, grade three or higher reported in the LAURA trial. Table 42 lists the relevant adverse event rates from the in LAURA trial for osimertinib and placebo and the associated AE utility decrement and duration. AE costs are applied as a one-off cost in the first model cycle, as a conservative assumption to avoid overestimating the impact of AEs.

Table 42: Rate of Grade ≥ 3 AE events and related disutilities used in the model

Adverse event	Osimertinib	Placebo	Disutility	Source	Duration (Days)	Source
Neutropenia	0.00%	1.37%	-0.09	Nafees et al. (2008) [100]	14.66	TA654[1]
Thrombocytopenia	0.70%	0.00%	-0.09	Assumed equal to neutropenia	14.66	TA654[1]
Decreased appetite	0.70%	0.00%	-0.07	Assumed same as fatigue	14.66	TA654[1]
Acute myocardial infarction	0.70%	0.00%	-0.03	Assumed same as myocardial infarction	14.00	Westwood et al. (2015)[101]
Left ventricular dysfunction	0.70%	0.00%	-0.03	Assumed same as myocardial infarction	14.00	Westwood et al. (2015)[101]
Myocarditis	0.70%	0.00%	-0.03	Assumed same as myocardial infarction	14.00	Westwood et al. (2015)[101]
Deep vein thrombosis	0.70%	0.00%	-0.01	Monahan et al. (2017) [102]	30.00	Monahan et al. (2017) [102]
Interstitial lung disease	0.70%	0.00%	-0.01	Assumed equal to pneumonitis	14.66	TA654[1]
Pleural effusion	0.00%	1.37%	-0.01	Assumed equal to pneumonitis	14.66	TA654[1]
Pneumonitis	1.40%	0.00%	-0.01	Goeree et al. (2016)[103]	14.66	TA654[1]
Pulmonary embolism	0.00%	1.37%	-0.01	Assumed equal to DVT	30.00	TA654[1]
Diarrhoea	1.40%	0.00%	-0.47	Nafees et al. (2008)[100]	5.53	Study CA046, TA306 (Taken from TA654)[1]

Adverse event	Osimertinib	Placebo	Disutility	Source	Duration (Days)	Source
Hepatic failure	0.70%	0.00%	-0.36	Assumed equal to decompensated cirrhosis. Crossan et al (2015)[104]	14.66	TA654[1]
Dry skin	0.70%	0.00%	-0.03	Nafees et al. (2008)[100]	14.66	TA654[1]
Rash maculo-papular	0.70%	0.00%	-0.03	Nafees et al. (2008)[100]	14.66	TA654[1]
Asthenia	0.70%	0.00%	-0.07	Nafees et al. (2008)[100]	23.78	PIX301 trial, TA476 (Taken from TA654)[1]
Alanine aminotransferase increased	0.70%	0.00%	-0.05	TA654[1]	14.66	TA654[1]
Blood creatine phosphokinase increased	0.70%	0.00%	-0.05	TA654[1]	14.66	TA654[1]
Electrocardiogram QT prolonged	0.70%	0.00%	-0.05	TA654[1]	14.66	TA654[1]
Gamma-glutamyl transferase increased	0.70%	0.00%	-0.05	TA654[1]	14.66	TA654[1]
Radiation pneumonitis	1.40%	0.00%	-0.01	Assumed equal to pneumonitis	14.66	TA654[1]

Abbreviations: AE, adverse event.

In alignment with the model presented for durvalumab in TA798,[16] an option to exclude the impact of AEs was considered in the model and presented as a scenario analysis.

B.3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

HRQoL data was available from the LAURA clinical trial and was utilised within the model for the PF health state in line with the NICE reference case. The estimated marginal mean and associated standard deviation were used as utility inputs to the model (Table 43). The results showed that there was not a significant difference of utility between different treatments.

The progression-free health state utility values from the FLAURA trial was used as the base case utility value for the PD health state in the model.[1] This was considered to be a more robust estimate of PD utility given the lower samples size in the LAURA PD setting (N= 102 in LAURA PD vs. N=486 in FLAURA PF).

There are some differences between the progression-free FLAURA and progressed-disease LAURA populations, notably that all patients in LAURA received CRT; however, it was considered clinically plausible that the utility values for these patients would be comparable. A scenario was tested using LAURA PD values (Table 69).

Table 43: Utility values used in the model

Health state	Mean	SD	Source
PFS	[redacted]	[redacted]	LAURA trial
PD base case	0.794	0.01	FLAURA trial
PD scenario analysis	[redacted]	[redacted]	LAURA trial

Abbreviations: PD, progressed disease; PFS, progression-free survival; SD, standard deviation.

B.3.4.6.1 Age-adjusted utility values

To account for the natural decline in utility with increasing age, HSUVs were adjusted based on the age of the model population using the regression formula published by Hernández Alava et al. (2022)[105]

Age-specific utilities were extracted from UK Utility Norms (2022),[97] based on data from the 2014 wave of the Health Survey for England, which is the most recent wave that included the EQ-5D-3L data. The expected EQ-5D-3L by sex and age for the UK are presented in Table 44, in which the average utilities by age were calculated based on the proportion of gender from LAURA trial (61% of females).[10] As the start age in the model was set as 61.4 years old to align with the median age in the LAURA population, the average utility at 61 years old was set as the baseline average utility (i.e. 0.831). The rates of decline in utility with increasing age at each age was calculated as:

$$Rate_n = \frac{utility\ at\ age\ n}{baseline\ utility}$$

Then patients' utility was assumed to decrease at the same rate as the general population utility, and the rates were applied to health state utility as each age.

For example, when patients were 70 years old, the general average utility was 0.795 as presented in Table 44. The rate of decline in utility was equal to 0.795/0.831 which is 0.956, therefore, the PFS and PD utility in 70 years old were equal to 0.84 (0.88*0.856) and 0.76 (0.80*0.856), respectively.

Table 44: Expected EQ-5D-3L utility by age and sex in the UK

Age	Males	Females	Average utility
30	0.923	0.904	0.912
50	0.879	0.856	0.867
70	0.817	0.781	0.795
90	0.738	0.672	0.694

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Index treatment acquisition costs

Drug acquisition costs for osimertinib were obtained from the BNF.[106] Table 45 provides the details regarding the available formulations, pack sizes and prices. A PAS price is applied and is reported below alongside the list price.

No index treatment costs were included in the placebo arm.

Table 45: Drug acquisition unit costs

Drug	Strength [21]	Pack size [21]	Formulation [21]	Pack price [21]
Osimertinib	80mg	30	Tablet	[redacted] (list price: £5,770)
Osimertinib	40mg	30	Tablet	[redacted] (list price: £5,770)

B.3.5.1.2 Duration of treatment

In the model, the treatment duration for osimertinib was derived from the extrapolated TTD curve using the TTD data from LAURA trial (see Section B.3.3.3). Meanwhile, the treatment duration placebo is set to zero as it is not applicable.

B.3.5.1.3 Dosing schedule

Drug acquisition costs were calculated for osimertinib only using the dosing schedule and treatment duration. Full details are provided in Table 46.

Table 46: Posology of comparators in the base case

Regimen	Drug and dose	Schedule	Duration	Source
Osimertinib	Osimertinib	QD 80 mg oral	Until progression or unacceptable toxicity	LAURA[10]
Placebo	-	-	-	LAURA[10]

Abbreviations: QD, once daily

B.3.5.1.4 RDI

The model applied a user-modifiable relative dose intensity (RDI) from the LAURA trial for osimertinib per study treatment stage. In the LAURA trial, the initial dose of osimertinib of 80 mg once daily (QD) could be reduced to 40 mg QD to allow for management of intraperitoneal (IP)-related toxicities. Once the dose was reduced to 40 mg QD, the patient remained on this regimen until termination from study treatment. Since the pack size and cost of two strengths of osimertinib are the same (Table 45), the dose reduction would does not affect drug acquisition cost.

B.3.5.1.5 Drug administration costs

Administration costs for first-line interventions are presented in Table 47. The administration cost of osimertinib was assumed to be equivalent to 12 minutes of pharmacist dispensing time. This approach was aligned with the ERG's recommendation in TA654[1] and TA761[3] for oral treatments. Placebo was assumed to require no drug administration.

Table 47: Drug administration costs

Drug	Cost item	Number per admin	Unit cost	Source
Osimertinib	Pharmacist dispensing (12 minutes)	1	£10	PSSRU 2023;[107] Calculated based on pharmacist hourly cost (£50) and adjusted for the 12-minute dispensing time
Placebo	-	-	-	

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.1.6 Subsequent treatment costs

The model accounts for different subsequent treatment options upon index treatment discontinuation. These are modelled as a single basket of treatments for a mean treatment duration upon entry to the PD health state. Drug costs were modelled only, as the survival impact is considered to be captured within the OS and post-PS curve of index treatments. This approach was consistent with previous TAs for previously treated advanced or metastatic NSCLC.[3, 16, 86]

B.3.5.1.6.1 Distribution of subsequent treatments following index treatment discontinuation

The subsequent treatment distributions in the model are presented in Table 48. The subsequent treatment basket composition was informed by 5 UK clinical experts during one-to-one interviews in November 2024.[15] This approach ensures that the distribution of subsequent treatments in the economic model is reflective of current UK clinical practice. Whilst the type and distribution of subsequent treatments received remains broadly in line with what was received in the trial (Section B.2.3.3.4), as indicated by UK clinical experts and the current treatment restrictions for patients who have been previously treated for locally advanced/metastatic disease, osimertinib will not be given following progression in patients who received osimertinib treatment following CRT. Therefore, no osimertinib subsequent treatment costs were assumed in the osimertinib arm.

Table 48: Subsequent treatment distribution applied in the economic model

	Osimertinib	Placebo	Source
% receiving at least 1 line of subsequent treatment following index treatment discontinuation	[redacted]	[redacted]	Averages across responses from clinical experts in the UK[15]
% receiving each treatment			
Docetaxel	[redacted]	[redacted]	Averages across responses from clinical experts in the UK[15]
Paclitaxel	[redacted]	[redacted]	
Pemetrexed	[redacted]	[redacted]	
Carboplatin	[redacted]	[redacted]	
Osimertinib	[redacted]	[redacted]	
Radiotherapy	[redacted]	[redacted]	
Atezolizumab	[redacted]	[redacted]	
Bevacizumab	[redacted]	[redacted]	
Afatinib	[redacted]	[redacted]	
Gefitinib	[redacted]	[redacted]	
% receiving 2 lines of subsequent treatment following index treatment discontinuation	[redacted]	[redacted]	Averages across responses from clinical experts in the UK[15]
% receiving each treatment			
Docetaxel	[redacted]	[redacted]	Averages across responses from clinical experts in the UK[15]
Paclitaxel	[redacted]	[redacted]	
Pemetrexed	[redacted]	[redacted]	
Carboplatin	[redacted]	[redacted]	
Osimertinib	[redacted]	[redacted]	
Radiotherapy	[redacted]	[redacted]	

	Osimertinib	Placebo	Source
Atezolizumab	[redacted]	[redacted]	Averages across responses from clinical experts in the UK[15]
Bevacizumab	[redacted]	[redacted]	
Afatinib	[redacted]	[redacted]	
Gefitinib	[redacted]	[redacted]	

B.3.5.1.6.2 Subsequent treatment duration

The subsequent treatment durations included in the model were retrieved from the relevant literature and validated during one-to-one interviews with clinicians (Table 49).[15] However, there is no evidence on the duration of osimertinib therapy in this setting (i.e., progressing post-CRT without prior osimertinib treatment). To inform this treatment duration, the modelled mean from the osimertinib monotherapy arm from the ongoing submission of osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR-positive advanced NSCLC (ID6328) was considered.[15, 108] This is based on the most recent RCT of osimertinib in this setting (FLAURA2, NCT04035486). In the one-to-one interviews conducted in November 2024, four out of five clinicians stated that they would expect placebo patients in the PPS setting in LAURA who receive osimertinib to be on treatment longer than those in the progression-free setting in FLAURA or FLAURA2, driven by the higher median PPS in LAURA (41.8 months) compared with osimertinib monotherapy OS in FLAURA2 (36.7 months). Although naïve cross-trial comparisons of endpoints measured from different timepoints within a trial are generally unreliable, particularly when influenced by differing distributions of subsequent therapy, the observed difference suggests that the patient populations in these trials differ. As a result, using the modelled mean from FLAURA2 is not representative of the treatment duration for patients randomised to placebo in the LAURA trial who subsequently receive osimertinib. On average, clinicians confirmed that using an additional 6 months to the modelled mean duration in FLAURA2 would be a reasonable and clinically plausible assumption to model the duration of osimertinib in the PPS setting (i.e., 36 months).

Table 49: Subsequent treatment duration

Treatment	Duration of treatment (number of 30-day cycles)	Duration of treatment source
Docetaxel	3.04	Kim et al., 2008[109]
Paclitaxel	3.04	Kim et al., 2008[109]
Pemetrexed	4.26	Mok et al. 2017[110]
Carboplatin	2.23	Socinski et al. 2018[111]
Osimertinib	[redacted]	[redacted]
Radiotherapy	1.00	Assume a single course of treatment
Atezolizumab	8.32	Socinski et al. 2018[111]

Treatment	Duration of treatment (number of 30-day cycles)	Duration of treatment source
Bevacizumab	6.80	Socinski et al. 2018[111]
Afatinib	4.59	Katakami et al. 2013[112]
Gefitinib	4.59	Katakami et al. 2013[112]

B.3.5.1.6.3 Subsequent treatment costs

The dosing schedule (Table 50) for each drug used in the subsequent lines was assumed to estimate the subsequent cost. For simplicity, no-vial sharing was assumed.

Table 50: Dosing schedule of subsequent treatment

Regimen	Schedule	Source
Docetaxel	Q3W 75 mg/m^2 IV	EMC.UK[113]
Paclitaxel	Q3W 175 mg/m^2 IV	EMC.UK[114]
Pemetrexed	Q3W 500 mg/m^2 IV	EMC.UK[115]
Carboplatin	Q3W 575 mg IV	EMC.UK[116]
Osimertinib	QD 80 mg oral	EMC.UK[11]
Radiotherapy	Once	
Atezolizumab	Q3W 1200 mg IV	EMC.UK[117]
Bevacizumab	Q3W 8 mg/kg IV	EMC.UK[118]
Afatinib	QD 40 mg oral	EMC.UK[119]
Gefitinib	QD 250 mg oral	EMC.UK[120]

Abbreviations: IV, intravenous; QD, once daily; Q3W, every 3 weeks.

For dosage of chemotherapies (e.g. docetaxel and paclitaxel) which were dependent on patient body surface area (BSA) or weight, patient characteristics from LAURA were used for the calculations as they were assumed to be comparable to the target population. The values are presented in Table 51, in which the BSA was estimated based on average mean height and weight

Table 51: Patient characteristics in the CEM

Parameter	Input	Source
Weight (kg)	62.3	LAURA trial population[10]
Height (cm)	160.80	LAURA trial population[10]
Body surface area (m^2)	1.67	Calculated based on average height and weight using the Mosteller formula $BSA = \sqrt{\{(\quad\}(height(cm) \times weight(kg))/3600)}$

Abbreviations: BSA, body surface area; CEM, cost-effectiveness model.

The unit costs of subsequent treatments were obtained from British National Formulary (BNF) provides the details regarding the available formulations, pack sizes and prices. The cost per regimen was estimated per 30-day cycle and multiplied by the treatment duration presented above.

Table 52: Drug acquisition unit costs of subsequent treatment

Drug	Strength	Pack size	Formulation	Pack price	Source
Docetaxel	20 mg	1	vial	£162.75	BNF[106]
Paclitaxel	100 mg	1	vial	£200.35	BNF[106]
Pemetrexed	100 mg	1	vial	£128.00	BNF[106]
Carboplatin	600 mg	1	vial	£232.64	BNF[106]
Osimertinib	80 mg	30	tablet	[redacted]	BNF[106]
Radiotherapy	-	1	-	£479.06	BNF[106]
Atezolizumab	1,200 mg	1	vial	£3,807.69	BNF[106]
Bevacizumab	100 mg	1	vial	£205.00	BNF[106]
Afatinib	40 mg	28	tablet	£2,023.28	BNF[106]
Gefitinib	250 mg	30	tablet	£2,166.10	BNF[106]

[redacted].

Abbreviations: BNF, British National Formulary.

Administration costs for subsequent treatment are presented in Table 53 . The administration cost per treatment cycle of oral drugs was assumed to be equivalent to 12 minutes of pharmacist dispensing time. The administration cost per treatment cycle of IV drugs was assumed to be equivalent to 60 minutes of simple parenteral administration.

Table 53: Administration costs for subsequent treatment

Drug	Cost item	Unit cost	Admins per treatment cycle	Source
Docetaxel	Simple parenteral administration	£418	1.00	SB12Z; NHS National Cost Collection 2023/2024[121]
Paclitaxel	Simple -parenteral administration	£418	1.00	SB12Z; NHS National Cost Collection 2023/2024[121]
Pemetrexed	Simple -parenteral administration	£418	1.00	SB12Z; NHS National Cost Collection 2023/2024[121]
Carboplatin	Simple -parenteral administration	£418	1.00	SB12Z; NHS National Cost Collection 2023/2024[121]
Osimertinib	Pharmacist dispensing (12 minutes)	£10	1.00	PSSRU 2023[107]
Radiotherapy	Simple parenteral administration	£418	1.00	SB12Z; NHS National Cost Collection 2023/2024[121]
Atezolizumab	Simple parenteral administration	£418	1.00	SB12Z; NHS National Cost Collection 2023/2024[121]
Bevacizumab	Simple Parenteral administration	£418	1.00	SB12Z; NHS National Cost Collection 2023/2024[121]
Afatinib	Pharmacist dispensing (12 minutes)	£10	1.00	PSSRU 2023[107]
Gefitinib	Pharmacist dispensing (12 minutes)	£10	1.00	PSSRU 2023[107]

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.1.6.4 Total subsequent treatment costs

The subsequent treatment costs per 30-day cycle are presented in Table 54. The cost was applied as one-off cost to osimertinib and placebo upon discontinuation of index treatment.

Table 54: Total subsequent treatment costs

Subsequent treatment	Drug acquisition (30-day cycle)	Drug administration (30-day cycle)	Total one-off cost	
			Osimertinib	Placebo
Docetaxel	£1,454.42	£597.14	£8,258	£61,306
Paclitaxel	£835.54	£597.14		
Pemetrexed	£1,525.17	£597.14		
Carboplatin (AUC5)	£318.50	£858.57		
Osimertinib	[redacted]	£10.40		
Radiotherapy	£479.06	£418.00		
Atezolizumab	£5,439.56	£597.14		
Bevacizumab	£1,368.38	£597.14		
Afatinib	£103.23	£76.45		
Gefitinib	£6.30	£57.34		

[redacted]

B.3.5.2 Health-state unit costs and resource use

As described in Section B.3.1.1, the SLR included a total of 35 publications, which reported on HCRU and costs for patients with NSCLC (Appendix G). Health care resource use from the NICE submission for maintenance therapy following successful platinum-based CRT in unresectable NSCLC patients (TA798) was deemed the most appropriate published source for HCRU data to inform the values in the PF health state due to the similar indication (i.e. first line NSCLC treatment following CRT). Similarly, for the PD health state, relevant published resource use data was identified from TA654 (FLAURA, osimertinib in advanced and metastatic NSCLC)[1].

Values from TA798 for the PF health state,[16] and TA654 for the PD health state[1] were validated and subsequently adjusted by five UK clinical experts in the treatment of NSCLC during one-to-one interviews.[15, 122] The average of these responses formed the final HCRU inputs used in the model, and are presented in Table 55.

In the PD state, there is a higher proportion of placebo patients (86% of those who progress) receiving subsequent therapy compared to the osimertinib patients (67% of those who progress), based on the LAURA trial. In the one-to-one clinician interviews,[15, 122] clinicians commented that patients on an active treatment would require more monitoring compared to those who are not on an active therapy. The cost for the placebo patients in the PD state have therefore been increased by 19%, representing the difference between those on and off subsequent treatment. This was considered a pragmatic approach to estimate the increased monitoring costs required for patients on-treatment in the progressed disease setting, and a scenario analysis has been included whereby the cost in the PD state are not increased for these patients.

Table 55: List of health states and associated annual HCRU in the economic model

Health states	Items	Value (Osimertinib)	Value (placebo)	Reference in submission
PFS	Outpatient oncologist visit	1st year: [redacted] 2nd year: [redacted] Years 3−5: [redacted]	1st year: [redacted] 2nd year: [redacted] Years 3−5: [redacted]	NICE TA798;[16] Clinical expert opinion in the UK
	MRI (head)	[redacted]	[redacted]	

Health states	Items	Value (Osimertinib)	Value (placebo)	Reference in submission
	CT scan (chest)	1st year: [redacted] 2nd year: [redacted] Years 3−5: [redacted]	1st year: [redacted] 2nd year: [redacted] Years 3−5: [redacted]	
	ECG (one off)	[redacted]	[redacted]	
PD	Outpatient oncologist visit	[redacted]	[redacted]	NICE TA654;[1]Clinical expert opinion in the UK
	Chest radiography	[redacted]	[redacted]	
	CT scan (chest)	[redacted]	[redacted]	
	CT scan (Other)	[redacted]	[redacted]	
	ECG	[redacted]	[redacted]	
	Community nurse visit	[redacted]	[redacted]	
	Clinical nurse specialist	[redacted]	[redacted]	
	GP surgery visit	[redacted]	[redacted]	
	MRI (head)	[redacted]	[redacted]	

Abbreviations: CT, computed tomography; ECG, electrocardiogram; GP, General Practitioner; PD, progressed disease; PFS, progression-free survival.; NICE, National Institute for Health and Care Excellence.

HCRU costs were obtained from the most recent NHS National Schedule of Costs 2023/2024,[121] where possible, the PSSRU Unit Costs Database[107] or inflated using the PSSRU inflation indices. The updated unit costs of healthcare resource use selected for the LAURA model are shown in Table 56.

Table 56: Unit costs of health care resources

Resource	Unit cost	Source
Outpatient oncologist visit	£193	NHS National Cost Collection 2023/2024,[121] WF01A, code 370
Chest radiography (X-ray)	£44.13	NHS National Cost Collection 2023/2024,[121] code DAPF, inflated to 2024 prices
CT scan (chest)	£121	NHS National Cost Collection 2023/2024,[121] code RD26Z
CT scan (other)	£121	NHS National Cost Collection 2023/2024,[121] code RD26Z
MRI (head)	£224	NHS National Cost Collection 2023/2024,[121] code RD05Z
ECG	£90	NHS National Cost Collection 2023/2024,[121] code EY50Z
Community nurse visit	£87.76	Band 8A (1-hour patient-related work) PSSRU 2023, inflated to 2024 prices[107]

Resource	Unit cost	Source
Clinical nurse specialist	£87.76	Band 8A (1-hour patient-related work) PSSRU 2023, inflated to 2024 prices[107]
GP surgery visit	£44.95	10-minute visit; PSSRU 2023, inflated to 2024 prices[107]

Abbreviations: CT, computed tomography; ECG, electrocardiogram; MRI, Magnetic Resonance Imaging; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

B.3.5.3 Adverse reaction unit costs and resource use

Costs for managing AEs of Grade 3 or higher were sourced from the NHS National Schedule of Costs 2023/24 where possible[121] and NHS National Schedule of Costs 2022/2023,[123] inflated to 2024 prices using PSSRU indices (Table 57).

AE unit costs for Grade 3 or higher AEs were applied as a one-off cost at treatment initiation cycle (i.e., the first cycle of the model).

Table 57: List of adverse reactions and summary of costs in the economic model

Adverse reactions	Value	Code	Source
Neutropenia	£730	WJ11Z	NHS National Cost Collection 2023/2024[121]
Thrombocytopenia	£1,036	SA12G-SA12K	NHS National Cost Collection 2023/2024[121]
Acute myocardial infarction	£695	VC38Z	NHS National Cost Collection 2023/2024[121]
Left ventricular dysfunction	£695	VC38Z	NHS National Cost Collection 2023/2024[121]
Myocarditis	£695	VC38Z	NHS National Cost Collection 2023/2024[121]
Deep vein thrombosis	£1,917.45	YQ51A-YQ51E	NHS National Cost Collection 22/23,[123] inflated to 2024 prices
Diarrhoea	£916	SA03G-SA05J	NHS National Cost Collection 22/23,[123] inflated to 2024 prices
Interstitial lung disease	£4,362.72	DZ25G&DZ25H	NHS National Cost Collection 22/23,[123] inflated to 2024 prices
Pleural effusion	£4,380.02	DZ16L-DZ16N	NHS National Cost Collection 22/23,[123] inflated to 2024 prices
Pneumonitis	£4,581.23	DZ11N-DZ11Q	NHS National Cost Collection 22/23,[123] inflated to 2024 prices
Pulmonary embolism	£8,306	DZ09J	NHS National Cost Collection 2023/2024[121]
Dry skin	£177	WF01A-B	NHS National Cost Collection 2023/2024[121]

Adverse reactions	Value	Code	Source
Hepatic failure	£4,581.23	DZ11N-DZ11Q	NHS National Cost Collection 22/23,[123] inflated to 2024 prices
Alanine aminotransferase increased	£0.00	NA	Assumed to be 0
Blood creatine phosphokinase increased	£0.00	NA	Assumed to be 0
Electrocardiogram QT prolonged	£0.00	NA	Assumed to be 0
Gamma-glutamyl transferase increased	0.00	NA	Assumed to be 0
Radiation pneumonitis	£4,581.23	NA	Assumed to be equal to pneumonitis

Abbreviations: NHS, National Health Service.

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 CNS metastasis

Additionally, the model considered the monitoring and treatment costs associated with CNS metastasis when progressing to the PD health state.

The exclusion of costs associated with CNS metastases was criticised by the ERG in a recently submitted technology appraisal, in TA761.[3] The ERG emphasised that CNS metastases have been shown to incur significant economic burden compared to patients without these events due to higher monitoring costs and resources.

The proportion of patients who experience CNS metastasis in the osimertinib and placebo group was informed by the LAURA trial. The details are listed in Table 58.

Table 58: Percentage of patients progressing due to CNS metastases

Comparators	Number of patients in LAURA trial	Number of patients with BICR confirmed progression	Number of patients with BICR confirmed CNS RECIST progression	% with PD and CNS metastases
Osimertinib	143	53	18	12.60%

Placebo	73	62	26	35.60%

Abbreviations: CNS, central nervous system.

The costs included in the base case were in line with the approach used in TA536,[124] wherein a conservative assumption on the distribution of treatments for managing CNS metastases was made (see Table 59), based on clinical expert opinion.

Table 59: The management of CNS metastases

Scenario	SRS	WBRT	Surgical resection	Steroids	Source
Conservative	20%	25%	0%	100%	TA536[124]
Middle ground	22.5%	25%	5%	100%	

Abbreviations: SRS, stereotactic radiosurgery; TA, technology appraisal; WBRT, whole brain radiotherapy.

The cost of management of progression due to CNS metastases, including stereotactic radiosurgery (SRS), whole brain radiotherapy, surgical resection (craniotomy) and steroids (dexamethasone), were included in the model as a one-off cost applied at progression and are listed in Table 60.

Table 60: Cost of management of progression due to CNS metastases

Management	Frequency	Unit Cost	Source
SRS	0.20	£3,366	NHS National Cost Collection 2023/2024,[121] AA71A-B - Stereotactic Intracranial Radiosurgery, for Neoplasms or Other Neurological Conditions, with CC Score 0-4+
WBRT	0.25	£5,200	Royal College of Radiologists 2019 (TA761)[3]
Surgery (Craniotomy)	0.00	£12,235	NHS National Cost Collection 2023/2024,[121]- Intracranial procedures for patients aged 19 years and over, weighted average (AA50A-C, AA51A-D, AA52A-D, AA53A-D, AA54A-C, AA55A-C, AA57A)
Steroids (dexamethasone)	1.00	£189.89	NHS National Cost Collection 2022/23:[123] PHCD00066, PHCD00215, PHCD00271 – dexamethasone intraocular implant, intra-erythrocyte, intravitreal implant (weighted average), inflated to 2024 prices

Abbreviations: SRS, stereotactic radiosurgery; TA, technology appraisal; WBRT, whole brain radiotherapy.

The costs of monitoring for progression due to CNS metastases were also included in the model. The unit cost of healthcare resource use items associated with CNS

metastasis monitoring was multiplied by the associated frequency to calculate the total cost incurred. Unit costs were sourced from the latest NHS National Schedule of Costs (2023/2024),[121] where possible, NHS National Schedule of Costs (2022/2023),[123] inflated to 2024 prices using the PSSRU indices and PSSRU (2023) (Table 61).

Table 61: Cost of monitoring progression due to CNS metastases

Cost Item	Frequency per cycle	Unit cost	Source
MRI scan	0.30	£224	NHS National Cost Collection 2023/2024,[121]: RD05Z – Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
Consultant/Oncology outpatient visit	0.50	£159	NHS National Cost Collection 2023/2024,[121]: 800 – Clinical Oncology (Previously Radiotherapy) consultant led outpatient attendance
General practitioner visit	0.90	£48.16	PSSRU 2022/23: GP consultation lasting 10 minutes (with qualification costs), inflated to 2024 prices
Cancer nurse visit	1.40	£109	NHS National Cost Collection 2023/2024,[121]: N10AF – Specialist Nursing, Cancer Related, Adult, Face to face
Full blood test	1.40	£3	NHS National Cost Collection 2023/2024,[121]: DAPS05 – Haematology
Biochemistry	1.40	£2	NHS National Cost Collection 2023/2024,[121]: DAPS04 – Clinical biochemistry
CT scan	0.40	£121	NHS National Cost Collection 2023/2024,[121]: RD26Z – Computerised Tomography Scan of three areas, with contrast
X-ray	0.50	£44.23	NHS National Cost Collection 2022/23:[123] DAPF – Direct Access Plain Film, inflated to 2024 prices

Abbreviations: CT, computerised tomography; MRI, magnetic resonance imaging; NHS, national health service.

B.3.5.4.2 End of life care costs

HCRU of terminal patient care was considered to be sufficiently different from the resource use during post-progression management of disease. Accordingly, end of life costs were included as a one-off cost, applied at the time of death. Costs were a weighted calculation of hospital, hospice and home care costs. The percentage weight for each calculation was taken from Brown et al. (2013)[125] and the unit costs were taken from the PSSRU 2023.[107] This approach was aligned with the FLAURA2 cost-effectiveness model. The costs are reported in Table 44. These values,

reported in Table 62, were assumed to be the same for patients on both treatment arms.

Table 62: End of life care costs

Item	Cost	Source
End of life care	£12,411	PSSRU 2023;[107] Resource use: Brown et.al. (2013),[125] inflated to 2024 prices

Abbreviations: PSSRU, Personal Social Services Research Unit.

B.3.6 Severity

Not applicable.

B.3.7 Uncertainty

Uncertainty in the model is explored in Section B.3.11. Uncertainty relating to the model parameters is assessed through probabilistic sensitivity analysis (PSA) in Section B.3.11.1 and deterministic sensitivity analysis (DSA) in Section B.3.11.2. Scenario analyses are also used to analyse the impact of uncertainty on model inputs and assumptions and are discussed in Section B.3.11.3.

B.3.8 Managed access proposal

This submission proposes routine commissioning for osimertinib patients, within its expected licensed population, for [redacted] This submission is based on the robust clinical evidence provided by the LAURA trial; however, it may become relevant for osimertinib to be considered as a candidate for the Cancer Drugs Fund (CDF) under a managed access agreement due to low OS maturity or if other areas of clinical uncertainty are identified during the appraisal process. Further OS data from the LAURA trial is expected [redacted] and may be able to address these uncertainties. The systematic anti-cancer therapy (SACT) dataset is able to capture this outcome and could also be considered for supplementary data collection; however, the timeframe of a managed access agreement would not be able to produce mature OS data for decision making.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

provides a list of all the base-case inputs which are varied in DSA and PSA and details the CI by which they were varied, and the distributions assumed. Any inputs not included in this table were not varied in DSA or PSA.

Table 63 provides a list of all the base-case inputs which are varied in DSA and PSA and details the CI by which they were varied, and the distributions assumed. Any inputs not included in this table were not varied in DSA or PSA.

Table 63: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Model setup parameters			
Time horizon	38.6 years	Fixed	Section B.3.2.2.2
Cycle length	30 days	Fixed	Section B.3.2.2.2
Discount rate – Costs	3.5%	LCI: 3.15%, UCI: 3.85% (Normal)	Section B.3.2
Discount rate - QALYs	3.5%		Section B.3.2
Baseline patient characteristics			
Starting age (years)	61.4 years	SE (10.95) (Log-normal)	Section B.3.2.1
Body weight (kg)	62.3 kg	SE (13.15) (Log-normal)	Section B.3.2.1
Height (cm)	160.80 cm	SE (8.27) (Log-normal)	Section B.3.2.1
Proportion of female	61.11%	SE (12.22%) (Log-normal)	Section B.3.2.1
Base case survival curve parameters			
Osimertinib Progression free -> Progressed	Weibull	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.2.1
Parameter 1	0.81		Section B.3.3.2.1
Parameter 2	71.30		Section B.3.3.2.1
Placebo: Progression free -> Progressed	Generalised Gamma	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.2.1
Parameter 1	1.28		Section B.3.3.2.1
Parameter 2	0.73		Section B.3.3.2.1
Parameter 3	-1.42		Section B.3.3.2.1
Osimertinib: Progressed -> Dead	Gompertz	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.2.3
Parameter 1	0.03		Section B.3.3.2.3
Parameter 2	0.02		Section B.3.3.2.3
Placebo: Progressed -> Dead	Gompertz		Section B.3.3.2.3

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Parameter 1	0.05	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.2.3
Parameter 2	0.00		Section B.3.3.2.3
Osimertinib PFS	Weibull	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.2.2.1
Parameter 1	0.83		Section B.3.3.2.2.1
Parameter 2	63.92		Section B.3.3.2.2.1
Placebo PFS	Generalised Gamma	Cholesky decomposition of variance-covariance matrix used	Section B.3.3.2.2.1
Parameter 1	1.31		Section B.3.3.2.2.1
Parameter 2	0.74		Section B.3.3.2.2.1
Parameter 3	-1.32		Section B.3.3.2.2.1
Time-to-treatment discontinuation	Weibull	Cholesky decomposition of variance-covariance matrix used	Appendix M
Parameter 1	0.78		Appendix M
Parameter 2	64.26		Appendix M
KM values used to model TTD (months)	[redacted]	LCI: 32.40 UCI: 39.60 (Lognormal)	Appendix M
TTD cap	120	LCI: 108.00 UCI: 132.00 (Lognormal)	Appendix M
Adverse event rates – Osimertinib			
Neutropenia	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Thrombocytopenia	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Decreased appetite	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Acute myocardial infarction	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Left ventricular dysfunction	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Myocarditis	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Deep vein thrombosis	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Interstitial lung disease	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Pleural effusion	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Pneumonitis	1.40%	LCI: 1.26% UCI: 1.54% (Beta)	Section B.3.4.5
Pulmonary embolism	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Diarrhoea	1.40%	LCI: 1.26% UCI: 1.54% (Beta)	Section B.3.4.5
Hepatic failure	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Dry skin	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Rash maculo-papular	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Asthenia	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Alanine aminotransferase increased	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Blood creatine phosphokinase increased	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Electrocardiogram QT prolonged	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Gamma-glutamyltransferase increased	0.70%	LCI: 0.63% UCI: 0.77% (Beta)	Section B.3.4.5
Radiation pneumonitis	1.40%	LCI: 1.26% UCI: 1.54% (Beta)	Section B.3.4.5
Adverse event rates – placebo			
Neutropenia	1.37%	LCI: 1.23% UCI: 1.51% (Beta)	Section B.3.4.5
Thrombocytopenia	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Decreased appetite	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Acute myocardial infarction	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Left ventricular dysfunction	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Myocarditis	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Deep vein thrombosis	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Interstitial lung disease	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Pleural effusion	1.37%	LCI: 1.23% UCI: 1.51% (Beta)	Section B.3.4.5
Pneumonitis	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Pulmonary embolism	1.37%	LCI: 1.23% UCI: 1.51% (Beta)	Section B.3.4.5
Diarrhoea	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Hepatic failure	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Dry skin	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Rash maculo-papular	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Asthenia	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Alanine aminotransferase increased	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Blood creatine phosphokinase increased	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Electrocardiogram QT prolonged	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Gamma-glutamyltransferase increased	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Radiation pneumonitis	0.00%	LCI: 0.00% UCI: 0.00% (Beta)	Section B.3.4.5
Adverse event disutilities			
Neutropenia	-0.0897	SE: 0.015 (Beta)	Section B.3.4.5
Thrombocytopenia	-0.0897	SE: 0.001 (Beta)	Section B.3.4.5
Decreased appetite	-0.0735	SE: 0.008 (Beta)	Section B.3.4.5
Acute myocardial infarction	-0.0250	SE: 0.008 (Beta)	Section B.3.4.5
Left ventricular dysfunction	-0.0250	SE: 0.008 (Beta)	Section B.3.4.5
Myocarditis	-0.0250	SE: 0.008 (Beta)	Section B.3.4.5
Deep vein thrombosis	-0.0134	SE: 0.008 (Beta)	Section B.3.4.5

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Interstitial lung disease	-0.0080	SE: 0.008 (Beta)	Section B.3.4.5
Pleural effusion	-0.0080	SE: 0.008 (Beta)	Section B.3.4.5
Pneumonitis	-0.0080	SE: 0.008 (Beta)	Section B.3.4.5
Pulmonary embolism	-0.0134	SE: 0.008 (Beta)	Section B.3.4.5
Diarrhoea	-0.4680	SE: 0.008 (Beta)	Section B.3.4.5
Hepatic failure	-0.3634	SE: 0.000 (Beta)	Section B.3.4.5
Dry skin	-0.0325	SE: 0.000 (Beta)	Section B.3.4.5
Rash maculo-papular	-0.0325	SE: 0.000 (Beta)	Section B.3.4.5
Asthenia	-0.0735	SE: 0.000 (Beta)	Section B.3.4.5
Alanine aminotransferase increased	-0.0509	SE: 0.000 (Beta)	Section B.3.4.5
Blood creatine phosphokinase increased	-0.0509	SE: 0.000 (Beta)	Section B.3.4.5
Electrocardiogram QT prolonged	-0.0509	SE: 0.000 (Beta)	Section B.3.4.5
Gamma-glutamyltransferase increased	-0.0509	SE: 0.000 (Beta)	Section B.3.4.5
Radiation pneumonitis	-0.0080	SE: 0.000 (Beta)	Section B.3.4.5
Adverse event: duration (days)			
Neutropenia	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Thrombocytopenia	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Decreased appetite	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Acute myocardial infarction	14.00	LCI: 12.60 UCI: 15.40 (Gamma)	Section B.3.4.5
Left ventricular dysfunction	14.00	LCI: 12.60 UCI: 15.40 (Gamma)	Section B.3.4.5
Myocarditis	14.00	LCI: 12.60 UCI: 15.40 (Gamma)	Section B.3.4.5
Deep vein thrombosis	30.00		Section B.3.4.5

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Interstitial lung disease	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Pleural effusion	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Pneumonitis	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Pulmonary embolism	30.00	LCI: 27.00 UCI: 33.00 (Gamma)	Section B.3.4.5
Diarrhoea	5.53	LCI: 4.98 UCI: 6.08 (Gamma)	Section B.3.4.5
Hepatic failure	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Dry skin	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Rash maculo-papular	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Asthenia	23.78	LCI: 21.40 UCI: 26.16 (Gamma)	Section B.3.4.5
Alanine aminotransferase increased	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Blood creatine phosphokinase increased	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Electrocardiogram QT prolonged	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Gamma-glutamyltransferase increased	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Radiation pneumonitis	14.66	LCI: 13.19 UCI: 16.13 (Gamma)	Section B.3.4.5
Drug administration costs (cost per 30 days (£))			
Osimertinib	£10	LCI: 9.00 UCI: 11.00 (Gamma)	Section B.3.5.1.5
Placebo	£0	LCI: 0.00 UCI: 0.00 (Gamma)	Section B.3.5.1.5
Health care resource use			
Progression-free: Osimertinib			
Outpatient oncologist visit: year 1	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Outpatient oncologist visit: year 2	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Outpatient oncologist visit: year 3+	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
MRI (head)	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (chest): year 1	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (chest): year 2	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (chest): year 3+	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
ECG	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Community nurse visit	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Clinical nurse specialist	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
GP surgery	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Progression-free: Placebo			
Outpatient oncologist visit: year 1	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Outpatient oncologist visit: year 2	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Outpatient oncologist visit: year 3+	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
MRI (head)	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (chest): year 1	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (chest): year 2	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (chest): year 3+	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
ECG	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Community nurse visit	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Clinical nurse specialist	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
GP surgery	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Progressed disease			
Outpatient oncologist visit	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Chest X-ray	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (chest)	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
CT scan (other)	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
ECG	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Community nurse visit	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Clinical nurse specialist	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
GP surgery	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
Acute Oncology service	[redacted]	SE ([redacted]) (Gamma)	Section B.3.5.2
MRI scan	[redacted]	LCI: [redacted] UCI: [redacted] (Gamma)	Section B.3.5.2
Health care resource use unit costs			
Progression-free			
Outpatient oncologist visit: year 1	£213.33	LCI:£192.00 UCI:£234.66 (Gamma)	Section B.3.5.2
Outpatient oncologist visit: year 2	£213.33	LCI:£192.00 UCI:£234.66 (Gamma)	Section B.3.5.2
Outpatient oncologist visit: year 3+	£213.33	LCI:£192.00 UCI:£234.66 (Gamma)	Section B.3.5.2
MRI (head)	£224.00	LCI:£201.60 UCI:£246.40 (Gamma)	Section B.3.5.2
CT scan (chest): year 1	£121.00	LCI:£108.90 UCI:£133.10 (Gamma)	Section B.3.5.2
CT scan (chest): year 2	£121.00	LCI:£108.90 UCI:£133.10 (Gamma)	Section B.3.5.2
CT scan (chest): year 3+	£121.00	LCI:£108.90 UCI:£133.10 (Gamma)	Section B.3.5.2
ECG	£90.00	LCI:£81.00 UCI:£99.00 (Gamma)	Section B.3.5.2
Community nurse visit	£87.76	LCI:£78.98 UCI:£96.54 (Gamma)	Section B.3.5.2
Clinical nurse specialist	£87.76	LCI:£78.98 UCI:£96.54 (Gamma)	Section B.3.5.2
GP surgery	£44.95	LCI:£40.46 UCI:£49.45 (Gamma)	Section B.3.5.2

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Progressed-disease unit costs			
Outpatient oncologist visit	£213.33	LCI: £200.00 UCI: £234.66 (Gamma)	Section B.3.5.2
Chest X-ray	£44.13	LCI: £39.72 UCI: £48.54 (Gamma)	Section B.3.5.2
CT scan (chest)	£121.00	LCI: £108.90 UCI: £133.10 (Gamma)	Section B.3.5.2
CT scan (other)	£121.00	LCI: £108.90 UCI: £133.10 (Gamma)	Section B.3.5.2
ECG	£316.83	LCI: £285.15 UCI: £348.51 (Gamma)	Section B.3.5.2
Community nurse visit	£87.76	LCI: £78.98 UCI: £96.54 (Gamma)	Section B.3.5.2
Clinical nurse specialist	£87.76	LCI: £78.98 UCI: £96.54 (Gamma)	Section B.3.5.2
GP surgery	£44.95	LCI: £40.46 UCI: £49.45 (Gamma)	Section B.3.5.2
Acute Oncology service	£0.00	LCI: £0.00 UCI: £0.00 (Gamma)	Section B.3.5.2
MRI scan	£224.00	LCI: £201.60 UCI: £246.40 (Gamma)	Section B.3.5.2
Monitoring costs			
Frequency per treatment cycle: osimertinib	1.00	LCI: 0.90 UCI: 1.10 (Gamma)	Section B.3.5.4
Frequency per treatment cycle: placebo	1.00	LCI: 0.90 UCI: 1.10 (Gamma)	Section B.3.5.4
Cost per treatment: osimertinib	£2.75	LCI: £2.48 UCI: £3.03 (Gamma)	Section B.3.5.4
Cost per treatment: placebo	£0.00	LCI: £0.00 UCI: £0.00 (Gamma)	Section B.3.5.4
Distribution of patients across first-line treatments			
From osimertinib	[redacted]	LCI: [redacted] UCI: [redacted] (Beta)	Section B.3.5.1.6.1
From placebo	[redacted]	LCI: [redacted] UCI: [redacted] (Beta)	Section B.3.5.1.6.1
Distribution of patients across second-line treatments			
From osimertinib	[redacted]	LCI: [redacted] UCI: [redacted] (Beta)	Section B.3.5.1.6.1
From placebo	[redacted]	LCI: [redacted] UCI: [redacted] (Beta)	Section B.3.5.1.6.1

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Subsequent treatment durations			
Docetaxel	3.04	LCI: 2.74 UCI: 3.34 (Lognormal)	Section B.3.5.1.6.2
Paclitaxel	3.04	LCI: 2.74 UCI: 3.34 (Lognormal)	Section B.3.5.1.6.2
Pemetrexed	4.26	LCI: 3.83 UCI: 4.68 (Lognormal)	Section B.3.5.1.6.2
Carboplatin	2.23	LCI: 2.01 UCI: 2.45 (Lognormal)	Section B.3.5.1.6.2
Osimertinib (placebo arm)	[redacted]	[redacted]	Section B.3.5.1.6.2
Radiotherapy	1.00	LCI: 0.90 UCI: 1.10 (Lognormal)	Section B.3.5.1.6.2
Atezolizumab	8.32	LCI: 7.49 UCI: 9.15 (Lognormal)	Section B.3.5.1.6.2
Bevacizumab	6.80	LCI: 6.14 UCI: 7.48 (Lognormal)	Section B.3.5.1.6.2
Afatinib	13.90	LCI: 12.51 UCI: 15.29 (Lognormal)	Section B.3.5.1.6.2
Gefitinib	11.67	LCI: 10.50 UCI: 12.84 (Lognormal)	Section B.3.5.1.6.2
Distribution of subsequent treatments (first line)			
Osimertinib			
Docetaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Paclitaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Pemetrexed	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Carboplatin	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Osimertinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Radiotherapy	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Atezolizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Bevacizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Afatinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Gefitinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Placebo			
Docetaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Paclitaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Pemetrexed	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Carboplatin	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Osimertinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Radiotherapy	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Atezolizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Bevacizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Afatinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Gefitinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Distribution of subsequent treatments (second line)			
Osimertinib			
Docetaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Paclitaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Pemetrexed	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Carboplatin	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Osimertinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Radiotherapy	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Atezolizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Bevacizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Afatinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Gefitinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Placebo			
Docetaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Paclitaxel	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Pemetrexed	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Carboplatin	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Osimertinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Radiotherapy	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Atezolizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Bevacizumab	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Afatinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Gefitinib	[redacted]	SE ([redacted]) Dirichlet	Section B.3.5.1.6.2
Subsequent treatment costs per 30 days			
Docetaxel	£1,627.50	LCI: £1,464.75 UCI: £1,790.25 (Gamma)	Section B.3.5.1.6.4
Paclitaxel	£858.64	LCI:£772.78 UCI:£944.50 (Gamma)	Section B.3.5.1.6.4
Pemetrexed	£1,645.71	LCI:£1,481.14 UCI:£1,810.28 (Gamma)	Section B.3.5.1.6.4
Carboplatin	£332.34	LCI:£299.11 UCI:£365.57 (Gamma)	Section B.3.5.1.6.4
Osimertinib	£2,192.60	LCI:£1,973.34 UCI:£2,411.86 (Gamma)	Section B.3.5.1.6.4
Radiotherapy	£479.06	LCI:£431.15 UCI:£526.97 (Gamma)	Section B.3.5.1.6.4
Atezolizumab	£5,439.56	LCI:£4,895.60 UCI:£5,983.52 (Gamma)	Section B.3.5.1.6.4
Bevacizumab	£1,464.29	LCI:£1,317.86 UCI:£1,610.72 (Gamma)	Section B.3.5.1.6.4

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Afatinib	£2,890.40	LCI:£2,601.36 UCI:£3,179.44 (Gamma)	Section B.3.5.1.6.4
Gefitinib	£189.00	LCI:£170.10 UCI:£207.90 (Gamma)	Section B.3.5.1.6.4
Subsequent treatment: administration costs per 30 days			
Docetaxel	£597.14	LCI:£537.43 UCI:£656.85 (Gamma)	Section B.3.5.1.6.4
Paclitaxel	£597.14	LCI:£537.43 UCI:£656.85 (Gamma)	Section B.3.5.1.6.4
Pemetrexed	£597.14	LCI:£537.43 UCI:£656.85 (Gamma)	Section B.3.5.1.6.4
Carboplatin	£858.57	LCI:£772.71 UCI:£944.43 (Gamma)	Section B.3.5.1.6.4
Osimertinib	£10.40	LCI:£9.36 UCI:£11.44 (Gamma)	Section B.3.5.1.6.4
Radiotherapy	£418.00	LCI:£376.20 UCI:£459.80 (Gamma)	Section B.3.5.1.6.4
Atezolizumab	£597.14	LCI:£537.43 UCI:£656.85 (Gamma)	Section B.3.5.1.6.4
Bevacizumab	£597.14	LCI:£537.43 UCI:£656.85 (Gamma)	Section B.3.5.1.6.4
Afatinib	£76.45	LCI:£68.81 UCI:£84.10 (Gamma)	Section B.3.5.1.6.4
Gefitinib	£57.34	LCI:£51.61 UCI:£63.07 (Gamma)	Section B.3.5.1.6.4
CNS metastases management			
HCRU cost per 30-days	£267.51	LCI:£240.76 UCI:£294.26 (Gamma)	Section B.3.5.4.1
CNS intervention costs (one-off)	£1,973.17	LCI:£1,775.85 UCI:£2,170.49 (Gamma)	Section B.3.5.4.1
Terminal care/end of life unit costs			
End of life care costs (£)	£12,411.06	LCI:£11,169.95 UCI:£13,652.17 (Gamma)	Section B.3.5.4.2
Adverse event costs			
Neutropenia	£730.00	LCI:£657.00 UCI:£803.00 (Gamma)	Section B.3.5.3
Thrombocytopenia	£1,036.00	LCI:£932.40 UCI:£1,139.60 (Gamma)	Section B.3.5.3
Decreased appetite	£916.00	LCI:£824.40 UCI:£1,007.60 (Gamma)	Section B.3.5.3

Variable	Value	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Acute myocardial infarction	£695.00	LCI:£625.50 UCI:£764.50 (Gamma)	Section B.3.5.3
Left ventricular dysfunction	£695.00	LCI:£625.50 UCI:£764.50 (Gamma)	Section B.3.5.3
Myocarditis	£695.00	LCI:£625.50 UCI:£764.50 (Gamma)	Section B.3.5.3
Deep vein thrombosis	£1,917.45	LCI:£1,725.71 UCI:£2,109.20 (Gamma)	Section B.3.5.3
Interstitial lung disease	£4,362.72	LCI:£3,926.45 UCI:£4,798.99 (Gamma)	Section B.3.5.3
Pleural effusion	£4,380.02	LCI:£3,942.02 UCI:£4,818.02 (Gamma)	Section B.3.5.3
Pneumonitis	£4,581.23	LCI:£4,123.11 UCI:£5,039.35 (Gamma)	Section B.3.5.3
Pulmonary embolism	£8,306.00	LCI:£7,475.40 UCI:£9,136.60 (Gamma)	Section B.3.5.3
Diarrhoea	£916.00	LCI:£824.40 UCI:£1,007.60 (Gamma)	Section B.3.5.3
Hepatic failure	£4,581.23	LCI:£4,123.11 UCI:£5,039.35 (Gamma)	Section B.3.5.3
Dry skin	£177.00	LCI:£159.30 UCI:£194.70 (Gamma)	Section B.3.5.3
Rash maculo-papular	£177.00	LCI:£159.30 UCI:£194.70 (Gamma)	Section B.3.5.3
Asthenia	£916.00	LCI:£824.40 UCI:£1,007.60 (Gamma)	Section B.3.5.3
Alanine aminotransferase increased	£0.00	LCI:£.00 UCI:£.00 (Gamma)	Section B.3.5.3
Blood creatine phosphokinase increased	£0.00	LCI:£.00 UCI:£.00 (Gamma)	Section B.3.5.3
Electrocardiogram QT prolonged	£0.00	LCI:£.00 UCI:£.00 (Gamma)	Section B.3.5.3
Gamma-glutamyltransferase increased	£0.00	LCI:£.00 UCI:£.00 (Gamma)	Section B.3.5.3
Radiation pneumonitis	£4,581.23	LCI:£4,123.11 UCI:£5,039.35 (Gamma)	Section B.3.5.3
Health state utility values			
Progression-free	[redacted]	SD:[redacted]	Section B.3.4.6
Progressed disease	0.794	SD: 0.01	Section B.3.4.6

B.3.9.2 Assumptions

The main assumptions of the economic model, alongside supporting justification, and scenario analyses are presented in Table 64.

The focus of this table are the assumptions/inputs which are varied in scenario analyses.

Table 64: Base case model assumptions and scenarios

Model input and cross reference	Sources/assumption	Justification	Scenarios
General			
Patient characteristics	Patient characteristics (age and body surface area) were derived from LAURA and were assumed to be representative of EGFRm NSCLC patients in the UK	The results of the LAURA trial are expected to be generalisable to patients with locally advanced, unresectable EGFRm NSCLC in England[15]	N/A; patient characteristics were varied in the DSA
Time horizon	38.6 -year time horizon was used, to the population age of 100-years	Preference specified in NICE reference case	20 years
Discounting	Costs and health outcomes were discounted annually by 3.5%	Preference specified in NICE reference case	1.5% discount rate applied to costs and health outcomes
Intervention and comparators			
Comparator	Placebo was assumed to be the only relevant comparator	As per the LAURA trial,[10] ESMO expert consensus statements,[32] and UK clinical expert opinion[15]	N/A
Subsequent treatments	Docetaxel, Paclitaxel, Pemetrexed, Carboplatin, Radiotherapy, Atezolizumab, Bevacizumab, Afatinib and Gefinitib are included as subsequent treatment options in the base case	The subsequent treatments were informed by the LAURA trial[10] and validated with clinical experts[15, 122]	N/A
	Osimertinib is included as a subsequent treatment option for the placebo treatment arm. Osimertinib is assumed to be excluded as a treatment option for the osimertinib treatment arm.	Clinical experts reviewed the subsequent therapies and stated osimertinib would not be received if a patient had progressed on osimertinib[15]	N/A
Efficacy			

Model input and cross reference	Sources/assumption	Justification	Scenarios
TTD	TTD was not bounded by PFS, and captures those patients who discontinue Tx before progression.	To account for the time between the patient's disease progression and the initiation of alternative subsequent treatment	N/A
	TTD and PFS were informed by LAURA data that had been extrapolated over the model time horizon.	Typically, oncology studies use TTD to inform time on treatment rather than PFS. This assumption allowed for situations that may occur in clinical practice. Patients in PFS health state may discontinue osimertinib. Similarly, patients that progress may continue taking osimertinib.	
Costs			
Treatment discount	Osimertinib had a discount of [redacted]% applied to its list price. A discount of [redacted] was applied to the use of osimertinib in subsequent therapy, representing indication-specific discounts.	The discount rate is assumed to be identical across line of treatment in the model	N/A
Treatment wastage	Wastage was excluded from the model	Due to all treatments being fixed dose in the model.	N/A
Osimertinib drug acquisition cost	Calculated based on available formulations, pack sizes, unit costs, and price per mg, patients incur the cost of osimertinib for the duration of treatment	To account for the total cost of treating patients with osimertinib	The additional incremental background cost of osimertinib was removed to account for the high cost of osimertinib as background therapy as per NICE DSU guidance

Model input and cross reference	Sources/assumption	Justification	Scenarios
PFS and PD health state costs	Items deemed relevant to expert opinions informed the health state costs	Clinical opinions informed the resource use considered relevant to clinical practice	N/A
Administration costs	Placebo does not incur administration costs	Placebo was assumed to not require drug administration	N/A
Chemotherapy drug acquisition costs	Pack prices obtained from BNF are applied to Docetaxel, Paclitaxel, Pemetrexed, Carboplatin, Radiotherapy, Atezolizumab, Bevacizumab, Afatinib and Gefinitib	Preference specified in NICE reference case	N/A
Utility			
Health state utility values	The HSUVs were assumed to be adjusted for age over time, treatment agnostic, and applied directly to health states. The LAURA trial was used to inform the progression-free utility value. The FLAURA trial progression-free utility value was used to provide the progressed-disease utility value.	Given the low maturity of PPS data, particularly in the osimertinib arm, there is considerable uncertainty regarding the utility data in the PD state in LAURA. Therefore, the utility from the PF state in the FLAURA study was utilised,[1] as it aligns with the treatment stage of the PD state in the LAURA study	LAURA clinical trial value (PD)

Abbreviations: DSA, deterministic sensitivity analysis; DSU, decision support unit; EGFR, epidermal growth factor receptor; HSUV, health state utility values; NICE, National Institute for Health and Care Excellence ;NSCLC, non-small cell lung cancer; PD, progressed disease; PFS, progression-free survival; TBC, to be confirmed; TTD, time to discontinuation.

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base case results are presented in Table 65. Clinical outcomes and the disaggregated results are presented in Appendix J.

All results presented in Table 65 use the PAS price for osimertinib for the LAURA indication. For subsequent treatments the PAS price for the FLAURA indication is used for osimertinib. List prices are used for all other treatments, including chemotherapy and subsequent treatments. The base case results show that osimertinib is associated with an increase of [redacted] life years, and [redacted] QALYs compared with placebo. Osimertinib is associated with an increase in costs of [redacted] versus placebo, based on the PAS price for osimertinib. This results in an ICER of £20,316 versus placebo.

The base case net health benefit at the £30,000 WTP threshold is shown in Table 66. The base case net health benefit shows a NHB of 0.580 at the £30,000 WTP threshold, based on the prices in the commercial access agreement for osimertinib.

Table 65: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,316

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 66: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £30,000
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	-
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	0.580

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

PSA was performed by varying parameters in the model simultaneously by sampling from probability distributions. The ranges and the distributions assumed are shown in Table 63. For parameters where CIs and/or standard deviations/standard errors of the mean were available, these are used to estimate parameter uncertainty. For variables where no CIs and/or SDs/SEs were available, the CIs are assumed arbitrarily to be +/-10% of the base case value, or other plausible maximum/minimum plausible ranges if +/-10% is implausible.

The results of the pairwise PSA are shown in Table 67. These results were generated based on 1,000 simulations (convergence of the ICER was achieved by the 56th simulation). The PSA results show osimertinib to be cost-effective at the £30,000 WTP threshold. The ICER is £18,748 in the probabilistic analysis, which is aligned with the deterministic analysis.

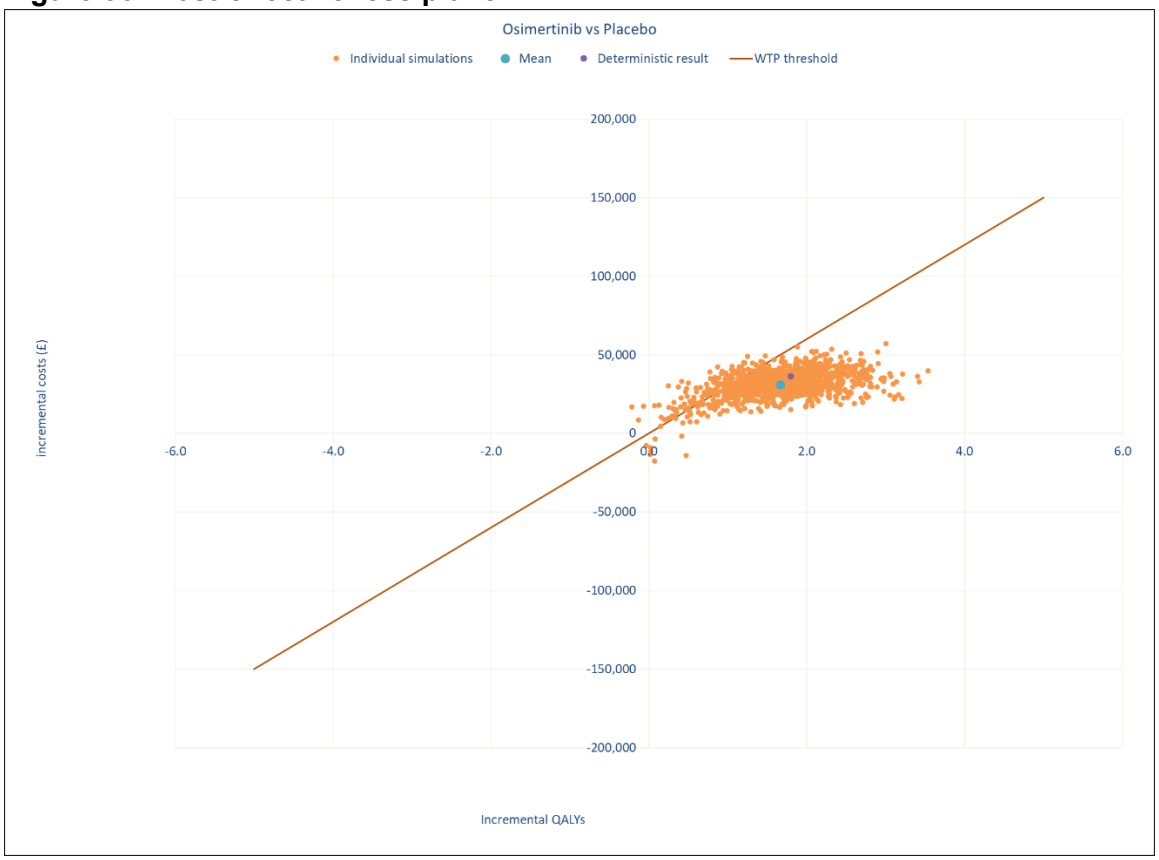
The results were plotted in a cost-effectiveness acceptability curve, which shows the probability of either treatment being the most cost-effective across a range of WTP thresholds (Figure 37). At a willingness-to-pay threshold of £30,000, osimertinib is associated with a 87.8% probability of being cost-effective.

Table 67: Base-case probabilistic incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,747.88	£18,747.88

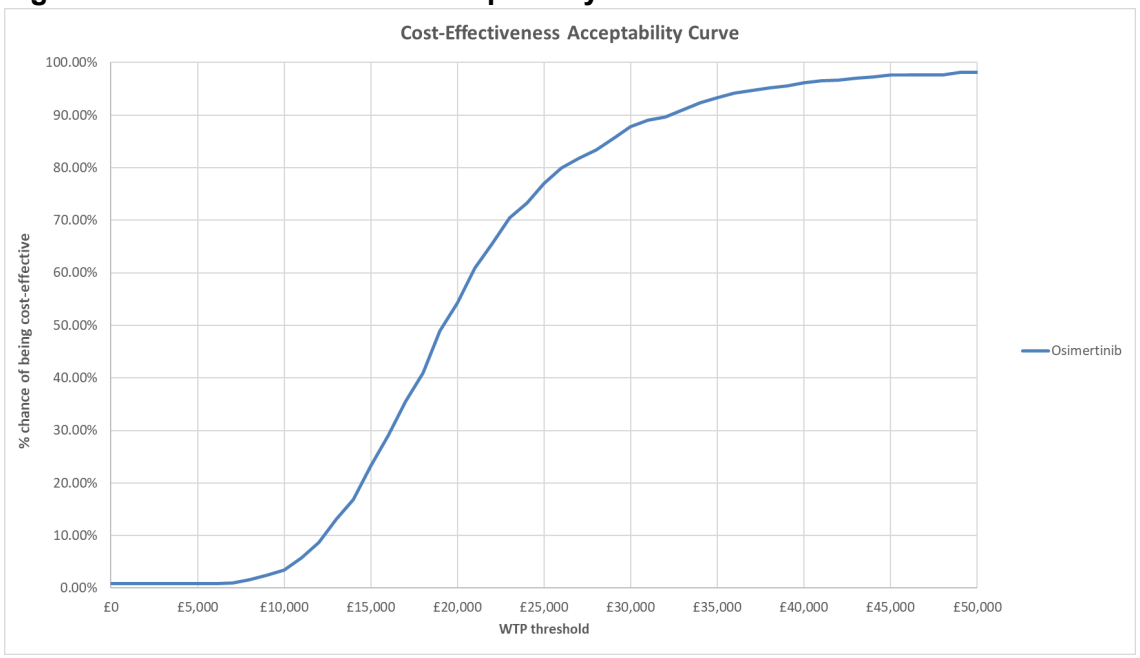
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 36: Cost-effectiveness plane



Abbreviations: QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 37: Cost-effectiveness acceptability curve



B.3.11.2 Deterministic sensitivity analysis

In the DSA, each input parameter was varied +/-10% (or other plausible maximum/minimum plausible ranges if +/-10% is implausible) to explore the impact of each parameter on model outcomes. Parameters with no associated uncertainty, such as drug costs, are excluded from the analysis. Interdependent variables that cannot be varied individually, such as efficacy extrapolation parameters, were also excluded. All parameters included in the one-way sensitivity analysis are presented in Table 63 and the results presented graphically in Figure 38.

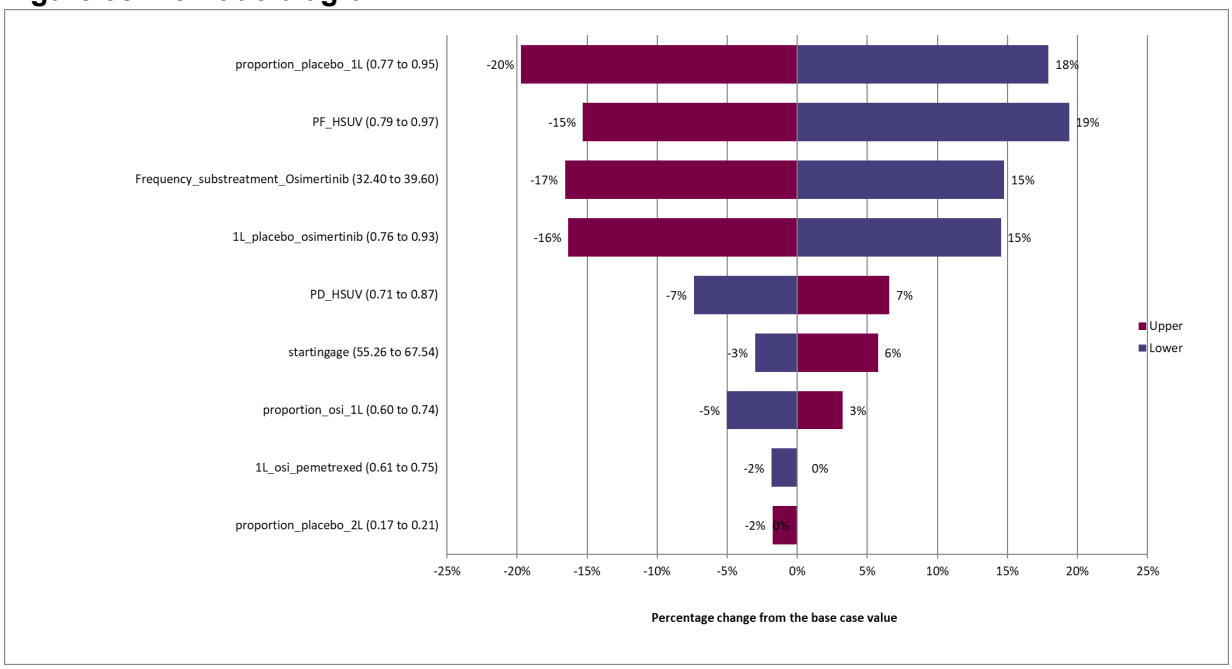
The results show that the most influential parameters on the model results are those that are related to the health state utilities (progression-free and progressed), proportion of patients transitioning from placebo to osimertinib as subsequent therapy and the proportion of patients receiving placebo as a first line treatment.

Table 68: DSA results for osimertinib vs placebo

Parameter	ICER with low value	ICER with high value	Difference (£)
Proportion receiving placebo 1L (0.77 to 0.95)	£23,956.55	£16,311.22	£7,645.33
Progression Free HSUV (0.79 to 0.97)	£24,259.40	£17,207.59	£7,051.81
Frequency of patients receiving Osimertinib as a subsequent treatment (32.40 to 39.60)	£23,316.00	£16,951.77	£6,364.22
Proportion of patients receiving Osimertinib as a 2L treatment after placebo 1L (0.76 to 0.93)	£23,271.24	£16,996.54	£6,274.70
Progressed disease HSUV (0.71 to 0.87)	£18,816.01	£21,650.27	-£2,834.26
Mean population age (55.26 to 67.54)	£19,704.47	£21,485.93	-£1,781.46
Proportion of patients receiving osimertinib 1L (0.60 to 0.74)	£19,295.38	£20,972.39	-£1,677.01
Proportion of patients receiving Osimertinib 1L that receive pemetrexed 2L (0.61 to 0.75)	£19,941.06	£20,326.71	-£385.64
Proportion of patients receiving placebo 2L (0.17 to 0.21)	£20,309.09	£19,958.68	£350.41
Osimertinib health state resource use in progressed disease (outpatient oncologist visit) (6.44 to 7.87)	£20,304.66	£19,963.11	£341.56

Abbreviations: HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; kg, kilogram; 1L, first line; 2L, second line.

Figure 38: Tornado diagram



Abbreviations: 2L, second line; ICER, incremental cost-effectiveness ratio.

B.3.11.3 Scenario analysis

To further explore the challenges relating to cost effectiveness of combination therapies and uncertainty around the modelled results, a series of scenario analyses were performed where specific alternative model assumptions were varied. The scenarios and results are outlined in Table 69. Key scenarios include varying the time horizon and discount rates, selection of alternative parametric models associated with time to progression and PFS for both osimertinib and placebo arms, and alternating the PD utility value to align with the PD value sourced from the LAURA clinical trial. In all scenario analyses, osimertinib was considered cost-effective versus placebo at a WTP threshold of £30,000 per QALY. Of note, the removal of the TTD cap (120 months) resulted in a 24.28% increase in the ICER versus the base case analysis and an ICER of £20,316 per QALY gained.

Table 69: Scenario analysis results for osimertinib vs placebo

Scenario	Osimertinib		Placebo		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change from base case ICER (%)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs				
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,316.44	-
Time horizon (20-years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,798.66	2.37%
Discount rates (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,805.63	-2.51%
Discount rates (6.0%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,684.53	1.81%
AE disutilities (excluded)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,312.75	-0.02%
Parametric models: Osimertinib: Time to progression and PFS: Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,161.64	-30.29%
Parametric models: Osimertinib: Time to progression and PFS: Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,319.67	9.86%
Parametric models: Placebo: Time to progression and PFS: Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,306.29	-9.89%
Parametric models: Osimertinib: PD -> Dead (PPS), Parametric models: Placebo: PD -> Dead (PPS): Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,233.83	-0.41%

Scenario	Osimertinib		Placebo		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Change from base case ICER (%)
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs				
(osimertinib), Weibull (placebo)								
PD utility value: LAURA PD value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,424.54	0.53%
Placebo PD cost: Equal to osimertinib arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,794.11	7.27%
Removal of the TTD cap of 120 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,248.89	24.28%

Abbreviations: AE, adverse event; ICER, incremental cost-effectiveness ratio; PD, progressed disease; PFS, progression-free survival; PPS, post-progression survival; QALY, quality adjusted life year.

B.3.12 Subgroup analysis

No subgroup analyses for osimertinib were considered to be relevant for the submission.

B.3.13 Benefits not captured in the QALY calculation

Due to the high burden of symptoms experienced in advanced and metastatic disease, patients with NSCLC may require physical or emotional support from caregivers.[56] The burden of care can negatively affect the caregivers ability to work and can impact them physically, emotionally, and financially.[57, 58] Osimertinib significantly improves PFS compared with placebo and may therefore have the potential to reduce the burden to caregivers in terms of their quality of life, time and effort required, and work productivity. The fear of progressing to a more advanced stage of disease also provides negative QoL impacts, with the limited treatment options at advanced disease stages resulting in an increased risk of deteriorating health and death.[126, 127]

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

Internal validation was performed by a senior health economist who was not involved in the development of the model. Validation consisted of the following:

- Systematically checking individual formulae on a sheet-by-sheet basis
- Cross checking input values against source references
- Ensuring transformation and derivation of model input values is as described and has been conducted correctly
- Testing functionality (including navigation and any other macros) for errors
- A check of the PSA and DSA including distributions used and rationales used for distribution choices.

In addition, the model approach, assumptions and parameter inputs were thoroughly validated with clinical experts.

B.3.15 Interpretation and conclusions of economic evidence

This *de novo* economic evaluation has estimated the cost-effectiveness of osimertinib versus placebo for patients with EGFR mutation-positive locally advanced, unresectable non-small-cell lung cancer after platinum-based chemoradiation. The results of the evaluation show that osimertinib is associated with an increase in life years of [redacted] additional years, and [redacted] additional QALYs compared with placebo. Osimertinib is associated with an increase in costs of [redacted] versus placebo. This results in an ICER of £20,316.44 versus placebo.

Scenarios were explored, including analysing the impact of alternative parametric distributions on the rate of progression and progression free survival and the impact of selecting the LAURA clinical trial progressed disease health state utility value. The analyses found that the scenario that modelled the lognormal distribution to estimate the time to progression and PFS for osimertinib had the greatest impact on the ICER, with a reduction in the ICER of 30.29%. All scenarios were cost-effective at the £30,000 per QALY WTP threshold.

The one-way sensitivity analysis showed that the main drivers of cost-effectiveness are the progression-free utility health state utility, the proportion of patients receiving osimertinib in 2nd line treatment after previously receiving placebo, the proportion of patients receiving placebo in 1st line and the progressed-disease health state utility.

The PSA showed that the probabilistic results are consistent with the deterministic results, and that osimertinib is associated with a 87.8% probability of being cost-effective at a WTP threshold of £30,000.

B.3.16 Strengths and limitations

The CEA presented as part of this submission leverages an existing model framework accepted in oncology and used in previous NICE appraisals for NSCLC. Clinical efficacy and safety data for the CEA was informed from the LAURA clinical trial, which is an ongoing, global, Phase 3, double-blind, placebo-controlled,

randomised study to assess the efficacy and safety of osimertinib therapy in patients with EGFR mutation-positive (Ex19del and/or L858R) NSCLC, whose disease has not progressed during or following definitive platinum-based CRT. The economic evaluation also benefitted from clinical input which validated several of the modelling assumptions through an advisory board and external stakeholder engagements.

One limitation of the CEA is the low data maturity in the LAURA trial. However, to address this limitation an STM model structure was identified and employed as an appropriate approach to address low data maturity as it allows for the OS endpoint to be extrapolated as a function of PFS and PPS. As such, the chosen STM structure is considered a strength of this analysis. The STM structure also has precedence in the locally advanced unresectable NSCLC disease setting, following CRT, and in other early lung cancer appraisals. Given the low OS maturity, external experts specialising in the treatment of NSCLC also agreed that the STM structure was appropriate, with the PSM approach deemed as less appropriate due to the low maturity of data.

To address any potential uncertainty in the model inputs and parametric model selections, clinical validation, and extensive sensitivity analyses, including PSA, DSA, and scenario analyses, were conducted.

B.3.17 Conclusions

The results of this CEA indicate that osimertinib is a cost-effective treatment when assessed against the NICE WTP threshold of £30,000 per QALY. It can be considered a cost-effective option versus placebo for the 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, from the perspective of the UK NHS and PSS. This conclusion was consistent across the PSA, deterministic analyses and all scenario analyses.

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK Public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional survival analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced or unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Summary of Information for Patients (SIP)

January 2025

File name	Version	Contains confidential information	Date
ID6223 Osimertinib LAURA SIP 15Jan25	1.0	No	15th January 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Osimertinib (TAGRISSO®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adults with epidermal growth factor receptor (EGFR) mutation-positive (exon 19 deletion or exon 21 [L858R] substitution, either alone or in combination with other EGFR mutations) locally advanced, unresectable (i.e. inoperable) non-small cell lung cancer (NSCLC) whose disease has not progressed after platinum-based chemoradiation (CRT).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The marketing authorisation for osimertinib in this indication is pending. Please refer to Section B.1.2 of the main submission document for more information.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK Limited engages with the following patient advocacy groups in lung cancer, with the aims of strengthening patient insights and responding to requests for information: EGFR Positive UK and Roy Castle Lung Cancer Foundation.

AstraZeneca UK is also a corporate supporter of UK Lung Cancer Coalition, which includes patient advocacy groups.

Funding provided to UK patient groups is published annually on our website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Lung cancer is the third most common cancer in the UK, with 49,229 cases diagnosed each year, and is the number one cause of cancer deaths.[1] Non-small cell lung cancer (NSCLC) is the most common form of lung cancer in England and Wales, accounting for 80–85% of all lung cancers.[2] Approximately 5–10% of NSCLC have changes (also known as mutations) within the EGFR gene;[3, 4] this gene produces a protein which controls the growth and multiplication of healthy cells. Mutations in the EGFR gene can result in more EGFR protein being produced than is needed, leading to faster cell growth and multiplication, which can in turn cause cancer. Two of the most common mutations in the EGFR gene are exon 19 deletions and exon 21 L858R point mutations; these account for around 90% of all cases of NSCLC with EGFR mutations;[5, 6] and are the focus of this appraisal. These changes are referred to as EGFRm throughout the submission documents. Compared with tumours without EGFRm, the presence of EGFRm is associated with faster disease progression and a higher rate of brain metastases.[7, 8]

Approximately 20–35% of people with lung cancer present with cancer that has spread beyond the original tumour and cannot be removed with surgery.[9] Cancer that has spread into nearby tissues or lymph nodes is described as locally advanced, and cancer that has spread to other organs in the body is described as metastatic.[10] Around 70% of people with inoperable locally advanced EGFRm NSCLC experience a relapse or progression to metastatic disease within 2 years with current treatment.[11-13] People who progress to metastatic disease have poor 5-year survival rates (24.9% vs 8.8%) compared with people with locally advanced disease.[14]

Symptoms of NSCLC typically develop once the cancer becomes more advanced and these can have a substantial impact on the quality of life of people with NSCLC. Common symptoms associated with advanced NSCLC include a persistent cough, coughing up blood, persistent breathlessness, unexplained tiredness and weight loss, repeated chest infections, jaundice, and pain on breathing or coughing.[15, 16] People who develop brain metastases may also experience additional symptoms which can have a significant impact on physical and psychological QoL such as seizures, speech problems, and memory problems.[17, 18] Furthermore, in the UK, people diagnosed with brain metastases have their driving licenses suspended, leading to loss of independence.[19]

Due to the high burden of symptoms experienced in advanced and metastatic disease, people with NSCLC may require physical or emotional support from caregivers.[20] The burden of care can

negatively affect the caregivers ability to work and can impact them physically, emotionally and financially.[21, 22]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

People may be diagnosed with lung cancer after seeing their GP about their symptoms.[23] In cases where the GP thinks symptoms could be caused by lung cancer, they will arrange tests to help make a diagnosis, which may include a chest x-ray and/or a CT (computed tomography) scan.[23] If these tests show anything abnormal, the GP will request a referral to a chest specialist.[23]

At the hospital, the specialist will explain any other tests that may be needed; these may include a PET-CT (positron emission tomography-computed tomography) scan and a biopsy.[23] In cases where a positive diagnosis for NSCLC is received, further examinations may be required to describe the size and position of the tumour, identify certain mutations in the cancer cells (such as EGFRm), and establish whether the cancer has spread outside of the lungs.[23] These tests will also help to determine the best treatment for the patient and whether their tumour is operable.[24]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

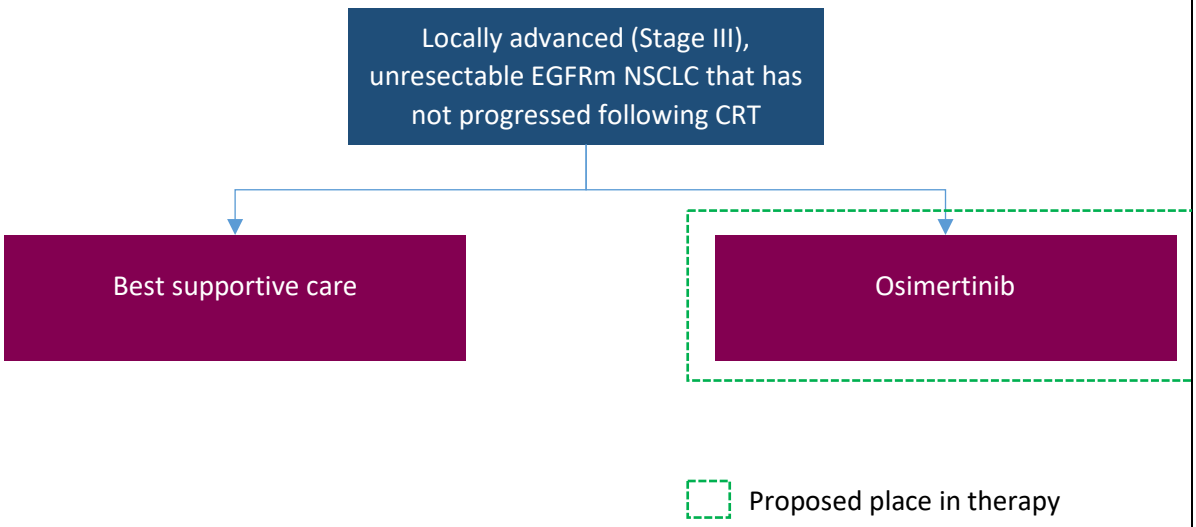
Chemoradiation (CRT; a combination of chemotherapy and radiation treatment) is the first treatment given to people with locally advanced, inoperable EGFRm NSCLC. There are currently no treatments recommended by NICE for people with EGFRm NSCLC after they have received platinum-based CRT, with people receiving active monitoring, also called best supportive care (BSC), which includes regular check-ups only to see if the cancer has returned or spread. No additional treatments are available to delay disease recurrence or progression to metastatic disease.

Following treatment with CRT, patients with locally advanced, inoperable NSCLC expressing EGFRm have a significantly higher likelihood of the cancer returning or spreading to other organs in the body (metastatic disease), compared with people with NSCLC who do not have EGFRm. Around 70% of EGFRm NSCLC patients experience recurrence or metastatic disease within 2 years of receiving CRT treatment.[11-13] As described in the previous section, progression to metastatic disease, particularly the development of brain metastases, is associated with a significant reduction in quality of life and survival.[1] There is therefore a substantial need for treatment for

people with locally advanced inoperable EGFRm NSCLC who have received CRT, to delay disease progression and maintain quality of life.

The proposed place of osimertinib in the current treatment pathway is presented in Figure 1.

Figure 1: Current treatment pathway for locally advanced unresectable EGFRm NSCLC with a proposed place in therapy for osimertinib



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

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Advanced NSCLC negatively affects quality of life due to the symptoms experienced as a result of the cancer and its treatment, and can worsen with progression to metastatic disease.[18, 25]

Studies that have looked into lived experiences showed that people with advanced NSCLC consider fatigue, pain and discomfort, shortness of breath, and cough to be their most important symptoms.[26, 27] Symptoms of the cancer have a negative impact on the physical and emotional wellbeing of those affected and impact their ability to carry out daily activities. Difficulty walking, anxiety/depression, impact on personal relationships, impact on sleep, and difficulty doing daily tasks have been identified as the most impactful for their lives.[26, 27]

The progression to metastatic disease and increasing symptom burden can also have a negative effect on mental health causing anxiety, depression, and feelings of demoralisation.[28, 29] People with metastases may also experience other negative symptoms that affect their quality of life; for

example, people with brain metastases may need assistance with daily tasks such as bathing, walking and driving.[30]

In addition, people with advanced or metastatic NSCLC may require physical or emotional support from caregivers.[20] This may be physically, emotionally and financially challenging for caregivers, negatively affecting their ability to work[21] and reducing their overall quality of life.[22]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The Summary of Product Characteristics for osimertinib is available here: https://www.medicines.org.uk/emc/product/7615/smpc

Osimertinib has been developed to permanently attach to mutated EGFR protein only. This can reduce growth and multiplication of the cancer cells. Osimertinib does not target normal EGFR protein on non-cancerous cells and so does not damage non-cancerous cells.[31, 32]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Osimertinib is not intended for use in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Osimertinib is available as 40 mg or 80 mg oral tablets, which can be taken at home. The recommended dose is 80 mg once a day.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
LAURA is a global clinical trial which has compared the efficacy and safety of osimertinib versus placebo (a treatment that does not contain an active drug ingredient, representing the current standard of care - active monitoring) in participants with locally advanced, inoperable EGFRm expressing NSCLC. Although some results from the trial are available, the trial is still ongoing. Results presented in this submission were based on the data analysis conducted in January 2024. LAURA included participants with inoperable EGFRm NSCLC whose cancer had spread to nearby tissues or lymph nodes (locally advanced disease). To be included in the study, participants must have undergone treatment with platinum-based CRT, with no evidence that since CRT their disease had got worse. In total, 143 participants received treatment with osimertinib and 73 participants received placebo. The outcomes measured in the trial included how long participants remained alive without their cancer getting worse (called progression-free survival in the trial), how long participants remained alive (called overall survival) and how long participants remained alive without the cancer that has spread to their brain getting worse (called central nervous system progression-free survival). Quality of life was also measured using a number of different questionnaires that were completed by the participants at different points during the trial. Any side effects reported by participants were also recorded. Further details on the study design and results from the LAURA trial are available from the following sources: 1. Lu S, Kato T, Dong X, Ahn MJ, Quang LV, Soparattanapaisarn N, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. N Engl J Med. 2024.[33] 2. Lu S, Casarini I, Kato T, Cobo M, Ozguroglu M, Hodge R, et al. Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non-small-cell Lung Cancer: LAURA Trial in Progress. Clin Lung Cancer. 2021;22(4):371-5.[34] 3. ClinicalTrials.gov. A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA) (LAURA). 2024. Available from: https://clinicaltrials.gov/study/NCT03521154#study-overview. Accessed on: 17th July 2024.[35]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition. In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.
The LAURA study showed that participants treated with osimertinib lived significantly longer without their cancer getting worse (median 38.9 months) than participants treated with placebo alone (median 7.3 months). In addition, there was a trend towards an improvement in how long

participants treated with osimertinib remained alive compared with participants treated with placebo; however, a lot of participants were still alive in both treatment groups and the trial will need to continue for longer for a final analysis of the difference in survival between the two treatments to be performed.

For participants who had brain metastases when starting treatment in the LAURA study, osimertinib provided a significant reduction (83%) in the risk of CNS disease progression or death. Furthermore, the number of participants with new CNS metastases was significantly lower with osimertinib treatment than in participants who received placebo.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life in LAURA was assessed using a number of different questionnaires that were completed by the participants at different time points during the study. These included questionnaires on the impact of having cancer (EORTC-QLQ-C30) and on specific issues that are known to affect people with lung cancer (EORTC QLQ-L13).

Results showed no difference in global health status/quality of life and physical functioning following treatment with either osimertinib or placebo. Importantly, the efficacy benefits of osimertinib were delivered with no negative impact of quality of life of study participants.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, osimertinib is associated with side effects. During the LAURA trial, nearly all participants experienced side effects (also called adverse events). The most commonly reported side effects for participants receiving osimertinib were radiation pneumonitis (48%), diarrhoea (36%), and rash (24%). The most commonly reported AEs for participants receiving placebo were the same; radiation pneumonitis (38%), diarrhoea (14%), and rash (14%). A summary of AEs which occurrent in 5% or more of either treatment groups is presented in **Table 1**. Rates of osimertinib discontinuation were low in both treatment groups (12.6% for osimertinib and 5.5% for placebo).

The proportions of participants who had an AE with outcome of death were low in both treatment arms (2.1% for osimertinib and 2.7% for placebo).

Table 1: Adverse events occurring in ≥5% of participants in the LAURA trial

Adverse event	Number (%) of patients	
	Osimertinib (N=143)	Placebo (N=73)
Patients with any AE	140 (98)	64 (88)
Radiation pneumonitis	68 (48)	28 (38)
Diarrhoea	51 (36)	10 (14)
Rash	34 (24)	10 (14)
COVID-19	29 (20)	6 (8)
Paronychia	24 (17)	1 (1)
Cough	23 (16)	7 (10)
Decreased appetite	21 (15)	4 (5)
Dry skin	18 (13)	4 (5)
Pruritis	18 (13)	5 (7)
Stomatitis	17 (12)	2 (3)
White blood cell count decreased	17 (12)	2 (3)
Pneumonia	16 (11)	6 (8)
Anaemia	14 (10)	3 (4)
Herpes zoster	13 (9)	2 (3)
Urinary tract infection	11 (8)	2 (3)
ALT level increased	10 (7)	2 (3)
Arthralgia	10 (7)	6 (8)
Upper respiratory tract infection	10 (7)	1 (1)
Acneiform dermatitis	9 (6)	2 (3)
Platelet count decreased	8 (6)	0
Dyspnoea	8 (6)	5 (7)
AST level increased	8 (6)	1 (1)
Nasopharyngitis	8 (6)	0
Pneumonitis	8 (6)	1 (1)
Sinus tachycardia	8 (6)	1 (1)
Productive cough	7 (5)	4 (5)
Musculoskeletal chest pain	5 (3)	9 (12)
Myalgia	5 (3)	6 (8)
Headache	2 (1)	4 (5)

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase.
Source: Lu et al. (2024).[33]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Following CRT treatment, people with locally advanced, inoperable EGFRm NSCLC have around 70% chance of their cancer coming back or progressing,[11-13] and this can have substantial impact on quality of life and survival.[1]The LAURA study showed that for locally advanced, inoperable EGFRm NSCLC, treatment with osimertinib significantly improves the time that people remain alive without their disease getting worse, with a trend towards an improvement in life expectancy, and reduces the risk of new brain metastases, compared with placebo.

People with EGFRm have a higher risk of developing brain metastases than those without EGFRm (70% vs 38%).[8] CNS metastases can have a substantial impact on symptom burden and QoL[18] and are associated with poor survival.[14] The results of the LAURA trial show that the risk of developing brain metastases is significantly lower for patients treated with osimertinib than for patients who receive placebo (the equivalent of active monitoring).

In addition, treatment with osimertinib in LAURA was well tolerated, with manageable side effects, and no negative impact on health-related quality of life when compared with placebo.

Osimertinib is taken orally at home.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Nearly all participants in both treatment arms experienced side effects. The proportion of participants that experienced a side effect that was considered to be caused by the treatment was higher in the osimertinib group (80.4%) compared with placebo alone (41.1%) as expected due to osimertinib being an active treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

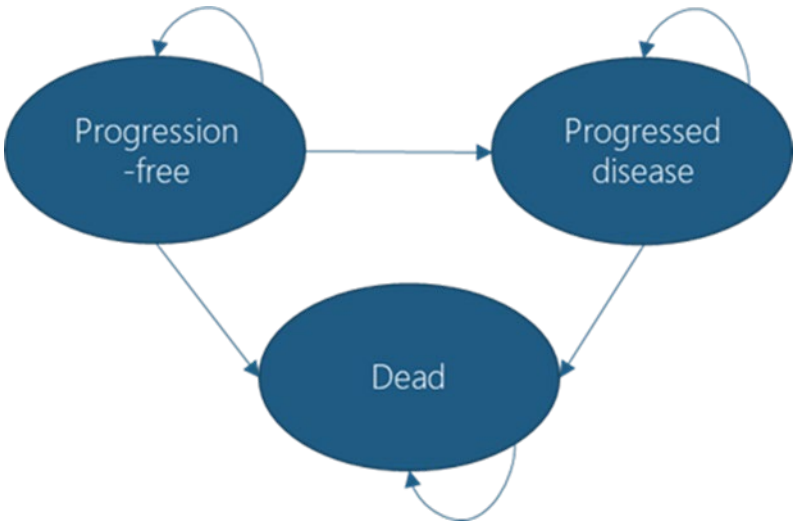
- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- An economic model was designed to simulate locally advanced or metastatic EGFRm NSCLC by modelling the different stages of the disease using categories called 'health states' (Figure 2). The health states used in the model were:
  - Progression-free – the cancer is not getting worse
  - Progressed – the cancer has got worse
  - Death
- In the model, patients start in the progression-free state, and then may either die, or experience worsening of the disease; once the patient has experienced worsening of the disease, they remain in this health state until they die. This reflects the real-life disease course
- The model compared the cost effectiveness of osimertinib with best supportive care (placebo) for the treatment of adult patients with locally advanced, inoperable EGFRm NSCLC whose disease had not progressed during or following CRT
- Patients experience different quality of life and accrue different costs depending on the health state they are in, with those in 'Progression-free' experiencing the best quality of life and lowest costs, and those in the 'Progressed' health state experiencing the worst quality of life and higher costs
- The model works by simulating how patients move between the health states when they are given different treatments; the more effective the treatment, the more time patients will spend in the 'Progression-free' health state

Figure 2: Model structure



Modelling how the treatment extends life

- Data from the LAURA trial were used to inform how long patients remained in the 'progression-free' or 'progressed' disease health states
- As data from the clinical trial were only available for a relatively short length of time, mathematical models were used to estimate the proportion of patients in each health state over the course of the patients' lifetime

Modelling how the treatment improves quality of life

- In the model, quality of life was determined by the health state that patients were in rather than the treatment they receive; patients in the 'progression-free' health state have a better quality of life than patients in the 'progressed' health state
- EQ-5D data from the LAURA trial were used to estimate the quality of life for patients in the 'progression-free' state while a previous NICE submission (TA621)[31] which evaluated osimertinib in people with advanced/metastatic EGFRm NSCLC was used to estimate the quality of life for patients in the 'progressed' health state
- The model also considered that side effects may have a negative impact on quality of life. The types of side effects and the number of patients experiencing them was informed by the LAURA trial, and the impact of these side effects on quality of life was estimated from the published literature
- Patients treated with osimertinib spend a longer time in the 'progression-free' health state compared with patients treated with placebo. This is associated with a better overall quality of life than the 'progressed' health state where patients may have experienced recurrent disease or development of metastases. As a result, osimertinib treatment leads to an overall improvement in quality of life for treated patients

Modelling how the costs of treatment differ with the new treatment

- Costs that were included in the cost-effectiveness model were those associated with treatment acquisition and administration, resource use (costs for healthcare professionals and hospitals), costs of treating side effects, and costs of any subsequent treatments that patients receive after they stop treatment with osimertinib or best supportive care upon disease progression
- CNS metastases are associated with increased resource use and costs. The model considered additional costs to monitor and treat CNS metastases when patients reached the 'progressed' state
- Osimertinib displays better efficacy compared with best supportive care. This translates into patients treated with osimertinib spending more time in the 'progression-free' health state, which is associated with lower costs of treatment and healthcare, over their lifetime, when compared with placebo

Uncertainty

- Uncertainty in the model inputs and structure was explored using sensitivity and scenario analyses; these analyses assessed the impact on the model outputs when inputs are varied by a defined amount

Cost-effectiveness result

- Osimertinib was found to have an ICER of £20,316 compared with placebo (best supportive care, defined as active monitoring).
- For full details on the modelled benefit in overall survival, progression-free survival, QALYs gained, and the incremental cost-effectiveness ratio, see the Company NICE Submission Document B, Section B.3.10.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Osimertinib represents the first targeted treatment option to maximise long-term outcomes for adults with locally advanced, inoperable EGFRm expressing NSCLC following treatment with platinum-based CRT who would otherwise receive active monitoring only. The use of osimertinib can delay disease progression without impacting quality of life for patients with locally advanced EGFRm NSCLC, including people who are considered higher risk such as those with CNS metastases.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Use of osimertinib is not expected to raise any equality issues.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Useful resources for NSCLC: • Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/lung-cancer • Macmillan Cancer Support: https://www.macmillan.org.uk/cancer-information-and-support/lung-cancer/non-small-cell-lung-cancer • NHS UK: https://www.nhs.uk/conditions/lung-cancer/ • Patient UK: https://patient.info/doctor/lung-cancer-pro • EGFR+ UK https://www.egfrpositive.org.uk/what-is-egfr Further information on NICE and the role of patients: • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- EGFR gene: A gene that makes a protein on cells that helps them grow
- EGFRm: Changes within the EGFR gene that can make cells grow too much and cause cancer
- Locally advanced cancer: Cancer that has spread into nearby tissues or lymph nodes
- Non-small cell lung cancer (NSCLC): One of two primary types of lung cancer and the most common kind
- Progression-free survival: The average length of time after the start of treatment in which a person is alive, and their cancer does not grow or spread
- Central nervous system (CNS) progression-free survival: The average length of time after the start of treatment in which a person is alive, and their brain cancer does not grow or spread
- Placebo: a treatment that does not contain an active drug ingredient

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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Updated overall survival data for Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced or unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

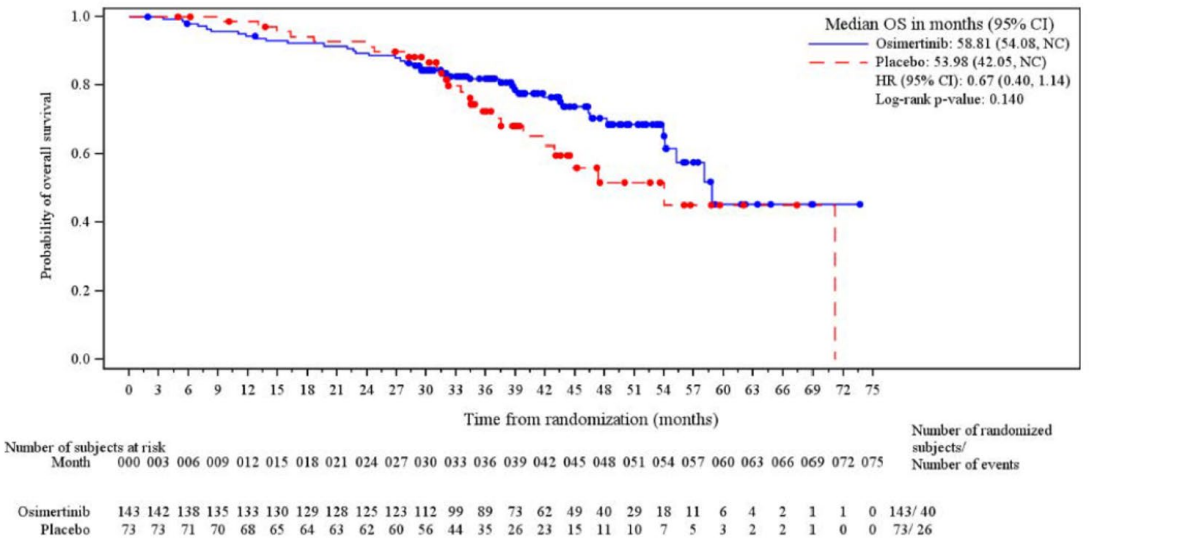
Overall Survival Update

In the Company submission made in January 2025 overall survival data (OS) presented showed an initial positive trend in following treatment with osimertinib compared with placebo. These data were taken from interim OS analysis (Data Cut Off [DCO]: 05 January 2024) at 19.9% maturity. Here we present updated OS from the LAURA study.

The updated data cut (DCO: 29th November 2024) provides more mature data (31% maturity), showing an improved and clinically meaningful OS benefit with osimertinib compared to placebo (median OS 58.8 months [95% confidence interval (CI) 54.1, not calculable (NC)] vs 54.0 months [95% CI 42.1, NC], respectively; hazard ratio 0.67; 95% CI 0.40, 1.14). The Kaplan Meier (KM) curves have been provided in Figure 1. These results included the significant crossover in the study with 78% of patients randomised to the placebo arm receiving treatment with subsequent osimertinib after progression.

These data further support the modelling assumptions made in the Company submission, and the clear separation in predicted OS. A comparison of the updated OS KM curves to the modelled OS curves in the Company submission base case are provided in Figure 2. Whilst the OS data were not used directly in the cost-effectiveness model, Figure 2 demonstrates that the model predicts OS well for osimertinib whilst over-predicting OS in the placebo arm.

Figure 1: Overall survival, Kaplan-Meier Plot (DCO 29 November 2024)



Circles indicate censored observations. The values at the base of the figure indicate number of patients at risk.
The HR (and 95% CI) and p-value were calculated using a log-rank test stratified by disease stage prior to chemoradiation (IIIA vs IIIB/IIIC) based on values entered into the interactive voice or web response system, after applying the SAP rule to collapse strata if there are <10 events per stratum. 2-sided p-value. A HR < 1 favors osimertinib to be associated with a longer OS than placebo.

Abbreviations: CI, confidence interval; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; NC, Not calculable, KM, Kaplan-Meier; NC, not calculable; OS, overall survival; SAP, statistical analysis plan.
DCO: 29 November 2024

Figure 2: Comparison of model-predicted OS vs. updated OS (DCO 29 November 2024)

Abbreviations: OS, overall survival; KM, Kaplan-Meier.

References

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Ramalingam, S.S. et al.
Journal of Thoracic Oncology, Volume 20, Issue 3, S123 - S124

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Clarification questions

February 2025

File name	Version	Contains confidential information	Date
ID6223_Osimertinib_EAG_clarification_letter_2025-02-21[CON]	1.0	Yes	21 February 2025

Notes for external assessment groups (EAGs) and NICE

[TL/TA to remove section when letter is completed]:

- Insert clarification questions using subheadings as required (see below).
- Style subheadings as 'heading 2' and questions as 'heading 3' so that they appear in the navigation pane.

Literature searching (heading 2 style)

- Indicate questions that are a priority using bold, as shown below.

Priority question: Please provide search strategies....(heading 3 style)

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

LAURA trial

A1. Please clarify whether LAURA trial participants were assessed for tumour PD-L1 expression levels at baseline. If so, please provide:

- the number and proportion of patients with tumour PD-L1 expression ≥1% and tumour PD-L1 expression <1%
- PFS (BICR- and investigator-assessed), CNS PFS (BICR- and investigator-assessed) and OS subgroup analysis results stratified by tumour PD-L1

expression levels (tumour PD-L1 expression ≥1% and tumour PD-L1 expression <1%)

Information on PD-L1 expression was not collected in the LAURA trial at baseline, and as described in Table 1 of the company submission, PD-L1 expression was not a pre-specified subgroup of the LAURA trial.

PD-L1 expression status does not influence treatment decisions for patients with EGFRm NSCLC. European Society for Medical Oncology (ESMO) expert consensus statements do not recommend immune checkpoint inhibitor (ICI) therapy in EGFRm patients post-CRT[1] and UK clinical experts consulted as part of an advisory board have stated that durvalumab is not routinely offered to patients with unresectable locally advanced EGFRm NSCLC in the UK.[2]

A2. Please provide CNS PFS (BICR- and investigator-assessed) and OS subgroup analysis results for the LAURA trial pre-specified subgroups (CS, Section 2.7).

Pre-planned subgroup analyses were conducted for the PFS endpoint in the LAURA trial only, as outlined in the study protocol.[3] The LAURA trial was not powered to detect significant differences between treatment arms for other endpoints.

A3. Please provide the results of proportional hazards assessments (i.e., Schoenfeld residuals plots and tests) for LAURA trial PFS, CNS PFS, OS and DoR data.

The proportional hazards assessment for PFS from the LAURA trial is presented in the company submission appendix (please see Section M1.1-M.1.2) A proportional hazards assessment for DoR was not conducted given that a Cox proportional hazards model was not fit to the data. Proportional hazards assessments for OS and CNS PFS are provided below.

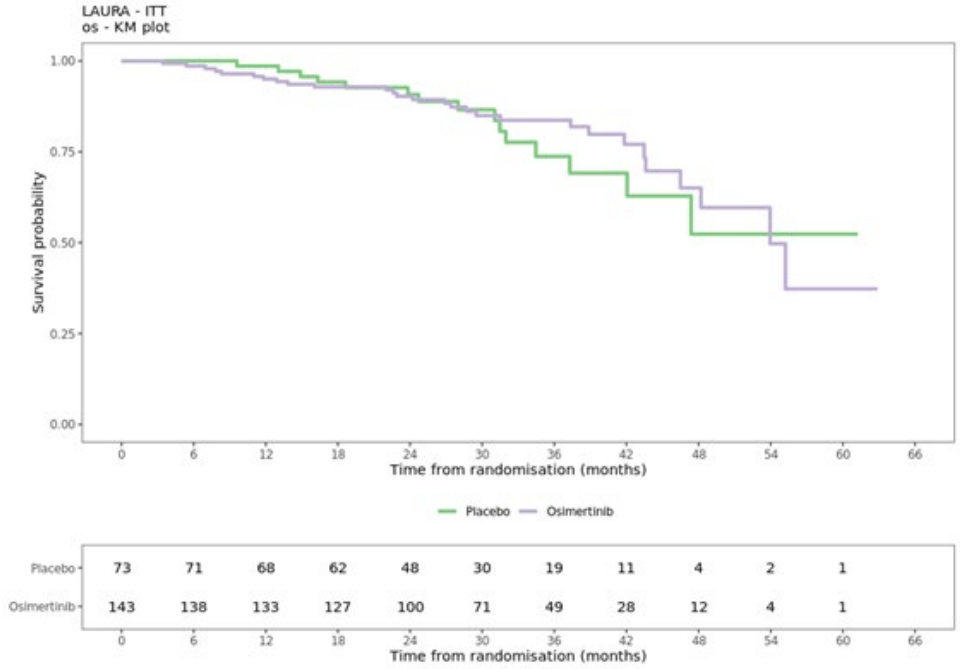
A3.1 Overall survival

Overall survival was defined as the time from the date of randomisation until death due to any cause. The OS Kaplan-Meier plot from the LAURA trial is presented in Figure 1.

Of the 143 patients in the osimertinib arm, 28 patients had died at the 05 January 2024 DCO. Median OS was 53.9 months (95% CI 53.9, NR). In total, 15/73 patients

in the placebo arm had died at the 05 January 2024 DCO. Median OS was NR (95% CI 46.5, NR).

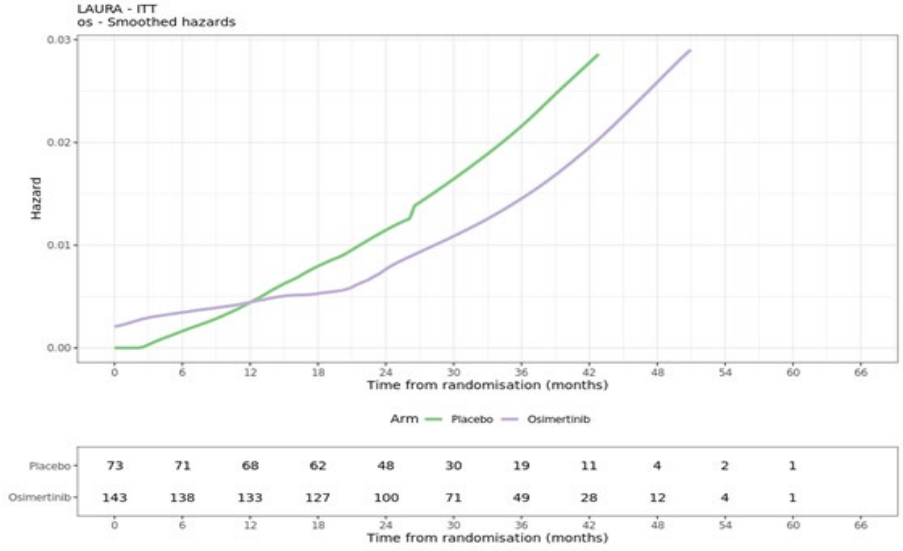
Figure 1: KM plot of OS from the LAURA trial



Abbreviations: ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival.

The smoothed hazards plot for OS is presented in Figure 2. The plot shows that the risk of an event over time increases for both the placebo and Osimertinib arm, with the risk of an event lower for Osimertinib from the 12-month time point post-randomisation.

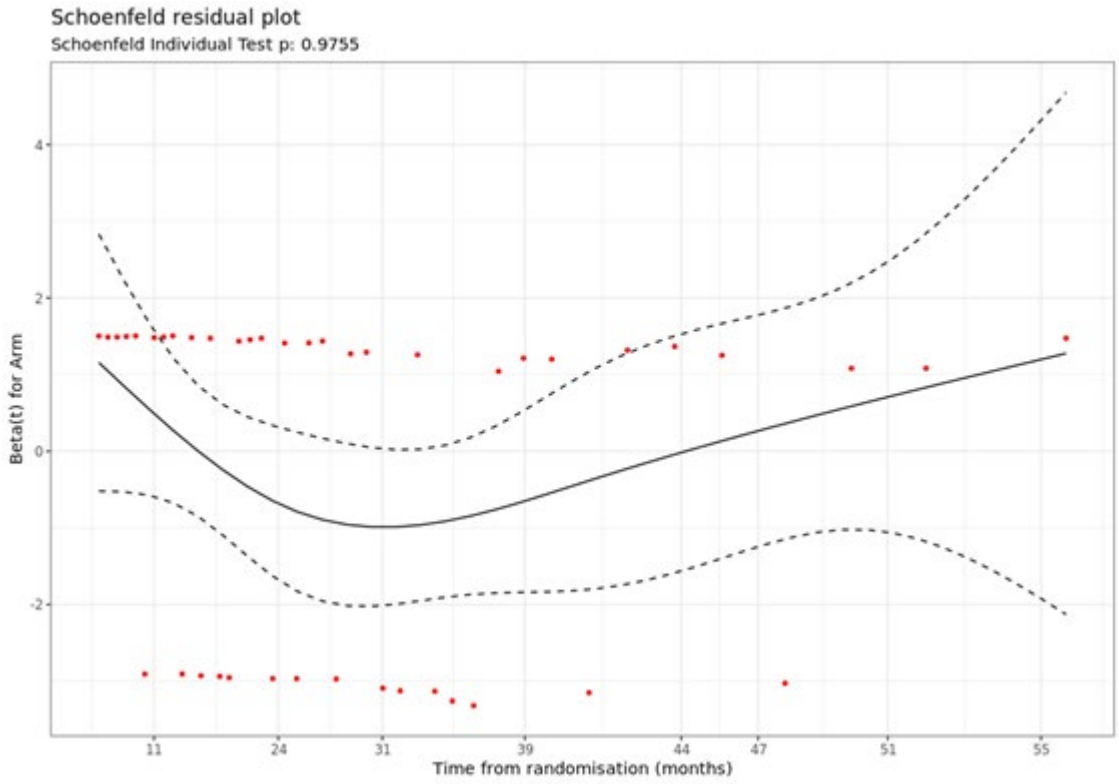
Figure 2: Smoothed hazard of OS for osimertinib and placebo from the LAURA trial



Abbreviations: ITT, intention to treat; OS, overall survival.

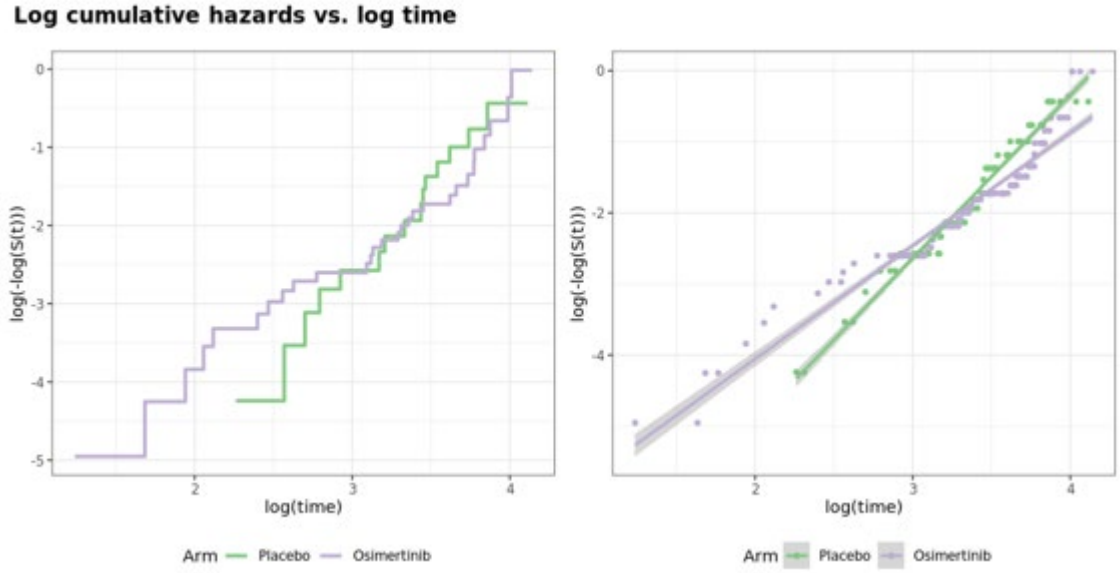
The plot of Schoenfeld residuals and log-cumulative hazard plot are shown in Figure 3 and Figure 4, respectively. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log cumulative hazards plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival.

Figure 3: Schoenfeld residual plot of OS



Abbreviations: OS, overall survival.

Figure 4: Log cumulative hazards of OS



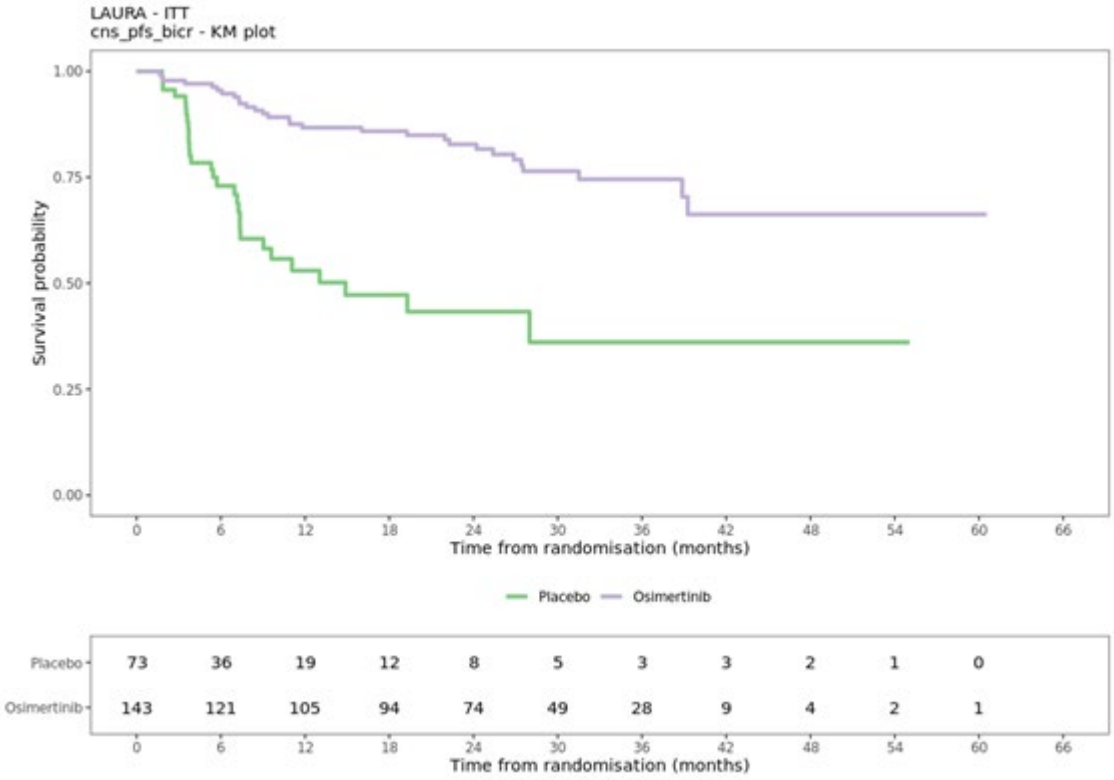
Abbreviations: OS, overall survival.

A3.2 CNS PFS

Central nervous system progression-free survival was defined as the time from randomisation until the date of CNS objective disease progression or death and was measured by neuroradiologist BICR. The CNS-PFS Kaplan-Meier plot from the LAURA trial is presented in Figure 5.

In total, 29/143 patients in the osimertinib arm had experienced CNS progression at the 05 January 2024 DCO. Median CNS PFS was not reached. In the placebo arm, 30/73 patients had experienced CNS progression (median 14.9 months [95% CI 7.4, NR]).

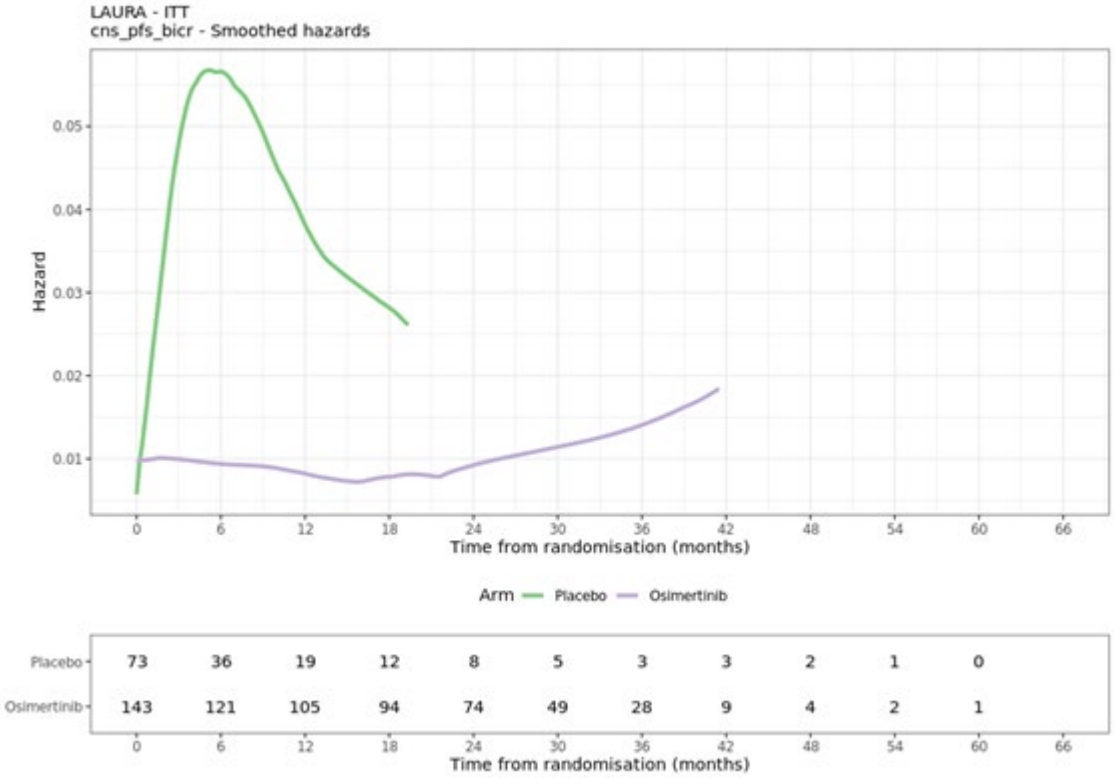
Figure 5: KM plot of CNS PFS from the LAURA trial



Abbreviations: BICR, blinded independent central review; CNS, central nervous system; ITT, intention-to-treat; KM, Kaplan-Meier; PFS, progression-free survival.

The smoothed hazards plot for CNS-PFS is presented in Figure 6. The risk of progression due to CNS increases sharply for the placebo arm, with a gradual decrease until the 19-month post-randomisation time point. The risk of progression for the placebo arm remains higher than the risk of progression for Osimertinib throughout the reported time period. The risk of progression in the Osimertinib arm is lower than placebo, with a slight increase over time.

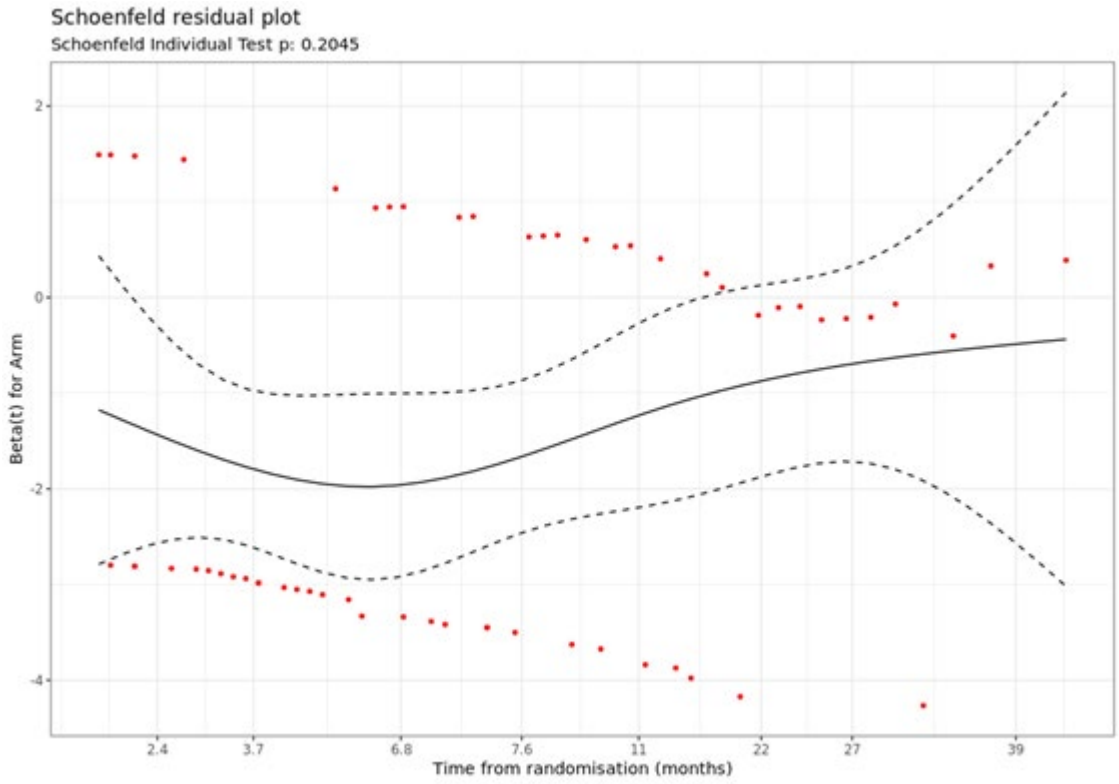
Figure 6: Smoothed hazard of CNS PFS for osimertinib and placebo from the LAURA trial



Abbreviations: BICR, blinded independent central review; CNS, central nervous system; ITT, intention-to-treat; KM, Kaplan-Meier; PFS, progression-free survival.

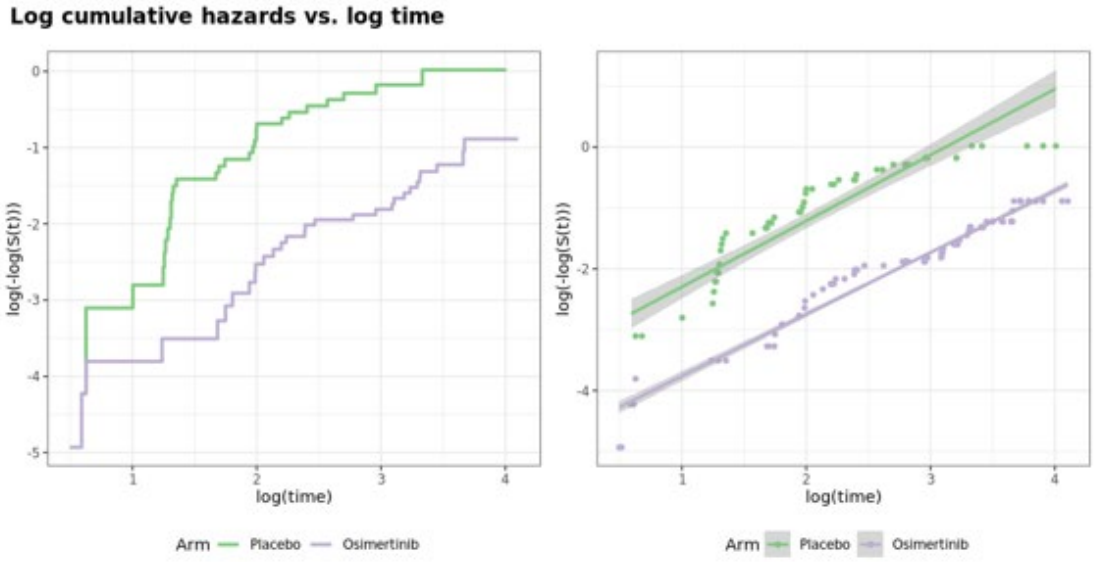
The plot of Schoenfeld residuals and log-cumulative hazard plot are shown in Figure 7 and Figure 9, respectively. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log cumulative hazards plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival.

Figure 7: Schoenfeld residual plot of CNS PFS



Abbreviations: CNS, central nervous system; PFS, progression-free survival.

Figure 8: Log cumulative hazard plot of CNS PFS



Abbreviations: CNS, central nervous system; PFS, progression-free survival.

A4. Please clarify at which timepoints EORTC QLQ-C30 and EORTC QLQ-LC13 data were collected and please provide the LAURA trial osimertinib and placebo arm

EORTC QLQ-C30 and EORTC QLQ-LC13 mean scores at baseline and at the subsequent assessment timepoints.

Data for the EORTC QLQ-C30 were collected at Week 4, Week 8 and thereafter every 8 weeks (±3 days) relative to randomisation. Data for the EORTC QLQ-LC13 were collected weekly up to Week 8, thereafter every 4 weeks (±3 days) relative to randomisation.[3]

EORTC QLQ-C30 global health status results at each time point are presented in Appendix Table 5. Results for each subscale/item at each timepoint can be found in Table 14.2.10.2.3 of the CSR appendices (page 366 to 575).[4] Results for the EORTC QLQ C13 subscales/items over time can be found in Table 14.2.10.2.4 of the CSR appendices, page 576 to page 845.[4]

Section B: Clarification on cost-effectiveness data

B1. Priority question. The EAG considers that, between 28 to 36 months, none of the fitted parametric distributions reflect the change in the within trial hazard of progression for the osimertinib arm (CS, Figure 19). The EAG also highlights that only the exponential distribution generates 10-year PFS estimates that are within the range suggested by clinicians at the company advisory board (10% to 15%) and does not represent the within trial hazard well. Please fit more flexible parametric distributions to LAURA trial osimertinib TTP and PFS data that more closely fit the within trial hazard and produce long-term PFS rates that are within the range suggested by clinicians. The EAG highlights that the NICE DSU TSD 21 outlines various adaptations (e.g., knot placement and number, incorporation of external data) that can be used to mitigate overfitting and produce different extrapolations.

Flexible splines with 1, 2 and 3 knots were fitted to the TTP and PFS K-M LAURA trial data following guidance from NICE DSU TSD 21.[1] As presented in Table 1 and Table 2 below, the three models with the best statistical fit according to Akaike Information Criterion (AIC) diagnostic are the 1-knot, 2-knot and 3-knot normal

splines. However, the AIC values for all splines are very similar, all within 2 points of each other.

Table 1: AIC/BIC for PFS

	AIC (rank)		BIC (rank)	
Model	**Placebo**	**Osimertinib**	**Placebo**	**Osimertinib**
Scale=hazard (1 knots)	397.5 (4)	569.5 (5)	404.4 (3)	578.4 (2)
Scale=hazard (2 knots)	398.3 (5)	569.4 (4)	407.5 (5)	581.3 (5)
Scale=hazard (3 knots)	399.8 (8)	570.2 (8)	411.2 (8)	585.0 (8)
Scale=normal (1 knots)	394.9 (1)	**568.0 (1)**	401.8 (1)	576.9 (1)
Scale=normal (2 knots)	396.8 (2)	**568.3 (2)**	406.0 (4)	580.1 (4)
Scale=normal (3 knots)	398.4 (7)	**569.2 (3)**	409.8 (7)	584.0 (7)
Scale=odds (1 knots)	396.9 (3)	569.7 (7)	403.7 (2)	578.6 (3)
Scale=odds (2 knots)	398.3 (6)	569.6 (6)	407.5 (6)	581.5 (6)
Scale=odds (3 knots)	399.9 (9)	570.4 (9)	411.4 (9)	585.2 (9)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.

Table 2: AIC/BIC for TTP

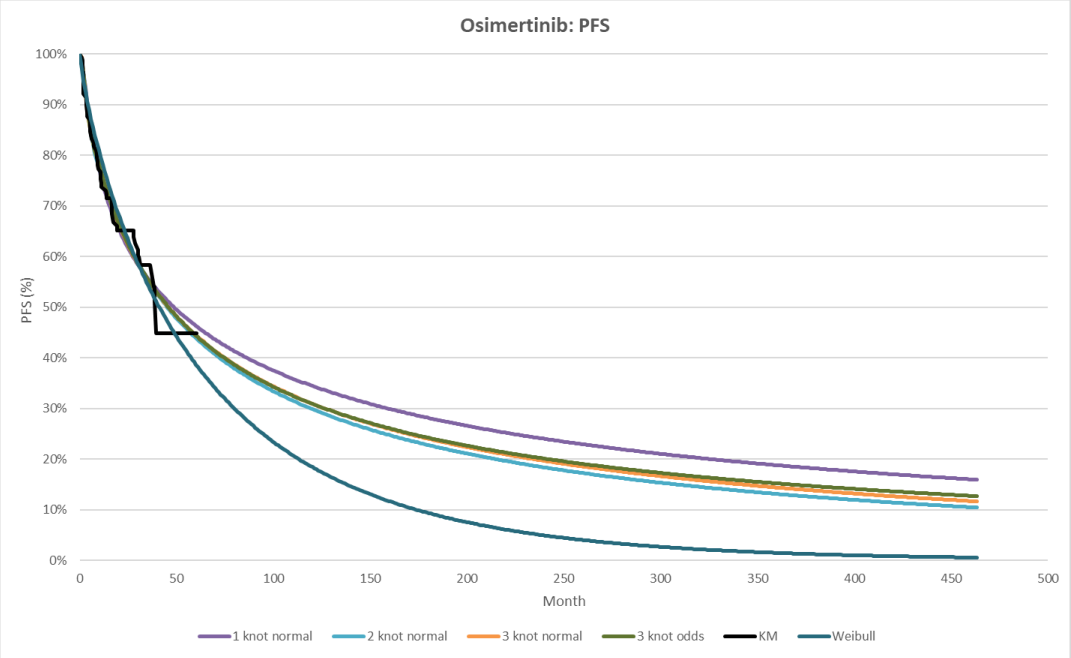
	AIC (rank)		BIC (rank)	
Model	**Placebo**	**Osimertinib**	**Placebo**	**Osimertinib**
Scale=hazard (1 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=hazard (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=hazard (3 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=normal (1 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=normal (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=normal (3 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=odds (1 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=odds (2 knots)	[redacted]	[redacted]	[redacted]	[redacted]
Scale=odds (3 knots)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.

The long-term extrapolations of the PFS data in the osimertinib arm using the 3 best fitting splines, the most pessimistic curve and the Weibull parametric model are presented in Figure 9. The flexible models all generate more optimistic long-term extrapolations than the Weibull, which is the base case parametric model for PFS and TTP extrapolations in the Company submission. For example, as shown on Figure 1 below, the 10-year PFS projections using the 3 best fitting splines are in the 30-35% range. This is substantially higher than the range suggested by clinicians

and the projections by the Weibull (18.8%). As such, the long-term extrapolations generated by the spline models are considered clinically implausible.

Figure 9: Long-term PFS extrapolation (osimertinib) - splines



Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

The long-term extrapolations of the TTP data in the osimertinib arm using the 3 best fitting splines, the most pessimistic curve and the Weibull parametric model are presented in Figure 10. These flexible models all generate more optimistic long-term extrapolations than the Weibull, which is the base case parametric model used in the submission.

Figure 10: Long-term TTP extrapolation (osimertinib) - splines

Abbreviations: KM, Kaplan-Meier; TTP, time-to-progression.

B2. Please explain why:

i. a piecewise approach (K-M data up to 36 months, parametric distribution thereafter) was considered appropriate to model LAURA trial osimertinib arm TTD data but was not appropriate to use to model other endpoints
ii. the exponential distribution was used to extrapolate TTD and why other parametric distributions were not considered

A piecewise approach (using Kaplan-Meier data up to 36 months and a parametric distribution thereafter) was deemed suitable for modelling the LAURA trial's osimertinib arm time-to-treatment discontinuation (TTD) data. This approach was taken in order to best capture the time on treatment within the LAURA trial whilst extrapolating appropriately and in line with clinical expectations.

The TTD curve could not be effectively modelled with a single extrapolation method that provided both statistical robustness and clinical credibility. Although the exponential distribution does not align well with the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores, upon clinical validation, it was regarded as the most plausible for UK clinical practice. Other trial endpoints

adequately matched the extrapolation through both statistical and clinical validation, thus not requiring a piecewise approach.

B3. In NICE TA654, publicly available information from the company submission provides the range of mean discounted life years for patients treated with osimertinib, in the company base case. Please confirm the mean discounted life years for osimertinib from TA654 under the committee's preferred assumptions. Additionally, please provide a comment on the consistency of life expectancy estimates between people treated with osimertinib in TA654 and those in this evaluation. If there are differences or similarities in life expectancy, please provide an overview and justification for these.

The total mean discounted life years for osimertinib from TA654 under the committee's preferred assumptions were [redacted] This compares with the total mean discounted life years of [redacted] in the osimertinib arm and [redacted] in the placebo arm of the current company submission.

The FLAURA trial, which informed TA654 included patients with previously untreated advanced EGFRm NSLC, of which 95% had metastatic disease (i.e. stage IV) at baseline, not all of which had CRT.[2] This contrasts with patients in the LAURA trial, where all patients in both treatment arms had locally advanced, unresectable (stage III) NSCLC at baseline.[3] As described in the company submission, patients with metastatic NSCLC have dramatically reduced 5-year survival compared with patients with locally advanced disease (24.9% vs 8.8%)[4] and therefore a direct comparison of life years gained between these two populations is not appropriate.

B4. In the company model, the PFS and PD utility values exceed or are close to the age and sex-matched general population utility value (0.831). Please comment on the plausibility of these values.

While the utility values used in the Company's base case may be greater than the utility of the age and sex-matched general population, similar studies have found

comparably greater utility values in similar patient populations. For example, Nafees et al. (2017) report that the utility for NSCLC patients of all ages, with stable disease and no adverse events, is 0.84.[6] This value is comparable to the utility values used for the PFS and PD health states in the Company model and thus further validates the chosen utility values.

B5. Please provide the mean osimertinib treatment duration for patients in the LAURA trial placebo arm who received osimertinib as a subsequent treatment (at the primary PFS analysis 5 January 2024 DCO).

An analysis of duration of treatment with osimertinib as a first subsequent therapy was conducted for both the osimertinib and the placebo arms of the LAURA trial.

For the placebo arm, the median duration of treatment was [redacted] and the restricted mean survival time was [redacted]. This median treatment duration is also comparable to the median duration of treatment used in the company submission ([redacted]), The LAURA median treatment duration was based on 50 patients in the placebo arm and only 16 events (23% maturity). Due to immaturity of the data, the mean value from the LAURA trial was not utilised in the economic model.

FLAURA2 and FLAURA were considered to inform this treatment duration in the model, however, based on a series of one-to-one interviews conducted in November 2024, four out of five clinicians stated that they would expect placebo patients in the PPS setting in LAURA who receive osimertinib to be on treatment longer than those in the progression-free setting in FLAURA or FLAURA2, driven by the higher median PPS in LAURA (41.8 months) compared with osimertinib monotherapy OS in FLAURA2 (36.7 months). As a result, using the modelled mean from FLAURA2 is also not representative of the treatment duration for patients randomised to placebo in the LAURA trial who subsequently receive osimertinib. On average, clinicians confirmed that using an additional 6 months to the modelled mean duration in FLAURA2 would be a reasonable and clinically plausible assumption to model the duration of osimertinib in the PPS setting (i.e., 36 months and data from FLAURA2 was deemed more appropriate.

B6. Please provide updated economic results using electronic Market Information Tool (eMIT) prices for the generic drugs listed in CS, Table 52.

The costs of docetaxel, paclitaxel, pemetrexed, carboplatin (AUC5) and gefitinib were available from the latest eMIT.[7] (Table 3)

Table 3:Cost of generics from eMIT

Name & PackSize	NPC Code	Quantity	Weighted Average Price	Standard Deviation of Price
Docetaxel 160mg/8ml solution for infusion vials (20mg/ml)/Packsize 1	DHC046	15,598.28	£19.70	£10.11
Paclitaxel 100mg/16.7ml solution for infusion vials/Packsize 1	DHA145	51,247.58	£12.89	£30.70
Pemetrexed 500mg powder for solution for injection vials (generic)/ Packsize 1	DEI020	9,674.54	£114.44	£127.31
Carboplatin 150mg/15ml solution for infusion vials /Packsize 1	DHE001	23,307.33	£12.18	£13.04
Gefitinib 250mg tablets/Packsize 30	DXA008	580.70	£60.68	£28.85

These have been incorporated in the economic model. As shown in Table 4 below, the incorporation of the price of generics into the model has a minimal impact on cost-effectiveness results, by slightly reducing the ICER down to £19,236. This is due to the higher proportion of generics in the subsequent lines of therapy in the osimertinib arm when compared with placebo.

Table 4: Base case results (with and without cost of generics)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER from base case
Original base case results							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,316	
Original base case results including costs of generics							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,236	-5.32%

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life years.

Section C: Textual clarification and additional points

C1. Please provide the LAURA trial CSR (5 January 2024 DCO), statistical analysis plan and trial protocol.

These have been included in the reference pack for this document with the following file names:

AstraZeneca LAURA CSR[8]

AstraZeneca LAURA CSR appendices[9]

AstraZeneca LAURA protocol and SAP[10]

C2. Please clarify how many independent reviewers completed the LAURA trial:

- data extraction
- quality assessment (CS, Section 2.5 and CS, Appendix D.3)

Information for each included article was extracted by a single reviewer in the first instance regarding both data extraction and quality assessment. A senior reviewer independently verified the extracted information and ensured that no relevant information had been missed. Any discrepancies or missing information identified by the senior reviewer were discussed until a consensus was reached and the missing data was extracted.

C3. Please provide a more detailed reference for the cost of radiotherapy presented in CS, Table 52.

The reference for the cost of radiotherapy in the economic model was cited as the BNF 2022. However, this was identified as an error. An up-to-date cost for radiotherapy delivery is available from the National Schedule of Reference costs, HRG code: SC24Z - Deliver a Fraction of Radiotherapy on a Megavoltage Machine using General Anaesthetic, elective inpatient stay.[11] The cost of £401 has been implemented into the model. It should be noted that the cost of radiotherapy is not considered a driver of cost-effectiveness and parameter uncertainty is not expected to have a substantial impact on the ICER. Updated base case ICER with the corrected cost of radiotherapy and cost of generics included is presented in Table 5.

Table 5: Base case results (corrected cost of radiotherapy added)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)	% change in ICER from base case
Base case results							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,316	
Cost of generics included							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,236	-5.32%
Cost of generics and corrected cost of radiotherapy included							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,225	-5.37%

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life years.

References

1. Rutherford MJ, Lambert PC, Sweeting MJ, Pennington B, Crowther MJ, Abrams KR, et al. NICE DSU Technical Support Document 21: Flexible models for survival analysis. Available at https://wwwsheffieldacuk/sites/default/files/2022-02/TSD21-Flex-Surv-TSD-21_Final_alt_textpdf. 2020.
2. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113-25.
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6. Nafees B, Lloyd AJ, Dewilde S, Rajan N, Lorenzo M. Health state utilities in non-small cell lung cancer: An international study. Asia Pac J Clin Oncol. 2017;13(5):e195-e203.
7. Gov.UK. Drugs and pharmaceutical electronic market information tool (eMIT). Available at https://wwwgovuk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.Accessed February 2025.
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9. AstraZeneca. Appendices of the clinical study report for osimertinib for the treatment of EGFR mutation-positive non-small cell lung cancer. A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre, International Study of Osimertinib as Maintenance Therapy in Patients with Locally Advanced, Unresectable EGFR Mutation-Positive Non-Small Cell Lung Cancer Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-Based Chemoradiation Therapy (LAURA)c. Data on file. 2024.
10. AstraZeneca. Clinical Study Protocol for a Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of osimertinib as maintenance therapy in patients with locally advanced, unresectable EGFR mutation-positive Non-Small Cell Lung Cancer (Stage III) whose disease has

not progressed following definitive platinum-based chemoradiation therapy (LAURA). Data on file. 2018.
11. NHS England. National schedule of NHS costs 2022/23. https://wwwenglandnhsuk/publication/2022-23-national-cost-collection-data-publication-2/. 2024.

Appendix

Table 6: EORTC QLQ-30 global health status, change from baseline over time – LAURA FAS

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
Global health status/QoL	Baseline	n	131	68
		Mean (SD)	72.07 (14.431)	71.69 (16.983)
		Median	75.00	70.83
		Min, Max	33.3, 100	33.3, 100
	Week 4	n	130	66
		Mean (SD)	65.83 (16.269)	74.75(17.600)
		Median	66.67	83.33
		Min, Max	16.7, 100	33.3, 100
		n change from Baseline	122	63
		Mean (SD) change from baseline	-6.56 (16.221)	2.25 (15.783)
		Min, Max change from baseline	-58.3, 33.3	-50.0, 33.3
Global health status/QoL	Week 8	N	129	59
		Mean (SD)	65.12 (17.732)	72.88 (19.853)
		Median	66.67	83.33
		Min, Max	0.0, 100	16.7, 100
		n change from baseline	120	56
		Mean (SD) change from baseline	-6.18 (17.336)	-0.60 (18.039)
		Min, Max change from baseline	-66.7, 33.3	-58.3, 50.0

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
	Week 16	n	119	48
		Mean (SD)	70.59 (16.375)	72.05 (14.226)
		Median	66.67	66.67
		Min, Max	33.3, 100	33.3, 100
		n change from baseline	109	45
		Mean (SD) change from baseline	-1.76 (17.753)	1.85 (18.022)
		Min, Max change from baseline	-58.3, 33.3	-33.3, 58.3
Global health status/QoL	Week 24	n	111	43
		Mean (SD)	69.52 (15.054)	69.38 (16.539)
		Median	66.67	66.67
		Min, Max	33.3, 100	33.3, 100
		n change from baseline	103	39
		Mean (SD) change from baseline	-2.51 (16.537)	-1.50 (20.844)
		Min, Max change from baseline	-50.0, 33.3	-33.3, 50.0
	Week 32	n	105	30
		Mean (SD)	70.24 (15.584)	68.89 (19.688)
		Median	66.67	66.67
		Min, Max	25.0, 100	16.7, 100
		n change from baseline	97	27
		Mean (SD) change from baseline	-2.58 (17.195)	-4.01 (19.932)
		Min, Max change from baseline	-58.3, 33.3	-33.3, 41.7
Global health status/QoL	Week 40	n	108	23

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
		Mean (SD)	70.68 (14.963)	68.48 (21.314)
		Median	66.67	75.00
		Min, Max	33.3, 100	25.0, 100
		n change from baseline	99	21
		Mean (SD) change from baseline	-1.43 (15.750)	-2.38 (19.745)
		Min, Max change from baseline	-50.0, 33.3	-41.7, 41.7
	Week 48	n	100	25
		Mean (SD)	72.58 (13.828)	71.33 (16.330)
		Median	70.83	75.00
		Min, Max	41.7, 100	41.7, 100
		n change from baseline	94	23
		Mean (SD) change from baseline	0.18 (13.879)	0.00 (19.462)
		Min, Max change from baseline	-33.3, 33.3	-33.3, 41.7
Global health status/QoL	Week 56	n	88	13
		Mean (SD)	71.88 (14.368)	73.72 (20.369)
		Median	66.67	83.33
		Min, Max	41.7, 100	33.3, 100
		n change from baseline	82	12
		Mean (SD) change from baseline	0.00 (15.101)	2.08 (19.824)
		Min, Max change from baseline	-50.0, 33.3	-25.0, 50.0
	Week 64	n	93	15
		Mean (SD)	72.85 (14.429)	67.22 (22.153)

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
		Median	66.67	66.67
		Min, Max	33.3, 100	25.0, 100
		n change from baseline	87	13
		Mean (SD) change from baseline	0.48 (14.342)	-3.85 (25.142)
		Min, Max change from baseline	-33.3, 33.3	-50.0, 41.7
Global health status/QoL	Week 72	n	90	13
		Mean (SD)	72.13 (15.511)	68.59 (21.558)
		Median	66.67	66.67
		Min, Max	33.3, 100	33.3, 100
		n change from baseline	83	12
		Mean (SD) change from baseline	-0.70 (14.907)	-3.47 (25.736)
		Min, Max change from baseline	-33.3, 33.3	-50.0, 50.0
	Week 80	n	88	9
		Mean (SD)	72.06 (15.579)	69.44 (21.651)
		Median	70.83	66.67
		Min, Max	33.3, 100	41.7, 100
		n change from baseline	81	8
		Mean (SD) change from baseline	-0.72 (14.919)	1.04 (25.369)
		Min, Max change from baseline	-41.7, 33.3	-33.3, 41.7
Global health status/QoL	Week 88	n	79	8
		Mean (SD)	74.26 (13.290)	63.54 (16.629)
		Median	75.00	66.67
		Min, Max	50.0, 100	33.3, 83.3

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
		n change from baseline	73	7
		Mean (SD) change from baseline	1.60 (14.004)	-3.57 (18.545)
		Min, Max change from baseline	-33.3, 33.3	-25.0, 25.0
	Week 96	n	79	6
		Mean (SD)	71.31 (15.775)	63.89 (22.153)
		Median	66.67	66.67
		Min, Max	33.3, 100	33.3, 83.3
		n change from baseline	73	5
		Mean (SD) change from baseline	0.34 (14.987)	1.67 (33.541)
		Min, Max change from baseline	-33.3, 33.3	-50.0, 41.7
Global health status/QoL	Week 104	n	71	8
		Mean (SD)	74.06 (15.010)	71.88 (14.042)
		Median	75.00	70.83
		Min, Max	33.3, 100	50.0, 91.7
		n change from baseline	66	7
		Mean (SD) change from baseline	2.78 (15.073)	4.76 (23.987)
		Min, Max change from baseline	-33.3, 33.3	-33.3, 41.7
	Week 112	n	63	4
		Mean (SD)	72.35 (14.954)	66.67 (19.245)
		Median	75.00	66.67
		Min, Max	33.3, 100	50.0, 83.3
		n change from baseline	58	3

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
		Mean (SD) change from baseline	1.15 (14.763)	13.89 (24.056)
		Min, Max change from baseline	-33.3, 33.3	0.0, 41.7
Global health status/QoL	Week 120	n	61	3
		Mean (SD)	70.90 (13.661)	75.00 (14.434)
		Median	66.67	83.33
		Min, Max	41.7, 100	58.3, 83.3
		n change from baseline	56	2
		Mean (SD) change from baseline	0.30 (14.031)	25.00 (23.570)
		Min, Max change from baseline	-33.3, 33.3	8.3, 41.7
	Week 128	n	52	2
		Mean (SD)	71.96 (14.102)	66.67 (23.570)
		Median	70.83	66.67
		Min, Max	33.3, 100	50.0, 83.3
		n change from baseline	48	2
		Mean (SD) change from baseline	1.04 (15.531)	20.83 (29.463)
		Min, Max change from baseline	-33.3, 41.7	0.0, 41.7
Global health status/QoL	Week 136	n	44	3
		Mean (SD)	73.86 (14.219)	69.44 (17.347)
		Median	75.00	75.00
		Min, Max	33.3, 100	50.0, 83.3
		n change from baseline	39	2
		Mean (SD) change from baseline	2.35 (16.329)	16.67 (23.570)
		Min, Max change from baseline	-50.0, 25.0	0.0, 33.3

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
	Week 144	n	39	3
		Mean (SD)	71.58 (18.007)	63.89 (20.972)
		Median	66.67	66.67
		Min, Max	16.7, 100	41.7, 83.3
		n change from baseline	36	2
		Mean (SD) change from baseline	1.85 (18.592)	8.33 (23.570)
		Min, Max change from baseline	-66.7, 33.3	-8.3, 25.0
Global health status/QoL	Week 152	n	35	2
		Mean (SD)	71.90 (18.423)	79.17 (5.893)
		Median	66.67	79.17
		Min, Max	16.7, 100	75.0, 83.3
		n change from baseline	32	1
		Mean (SD) change from baseline	4.43 (16.665)	41.67 (NC)
		Min, Max change from baseline	-33.3, 33.3	41.7, 41.7
	Week 160	n	30	2
		Mean (SD)	71.11 (15.588)	79.17 (5.893)
		Median	66.67	79.17
		Min, Max	33.3, 100	75.0, 83.3
		n change from baseline	27	1
		Mean (SD) change from baseline	2.78 (17.296)	41.67 (NC)
		Min, Max change from baseline	-33.3, 33.3	41.7, 41.7
Global	Week 168	n	22	3

Scale/Item	Timepoint	Statistic	Osimertinib (N=143)	Placebo (N=73)
health status/QoL				
		Mean (SD)	71.21 (18.496)	75.00 (14.434)
		Median	70.83	83.33
		Min, Max	16.7, 100	58.3, 83.3
		n change from baseline	19	2
		Mean (SD) change from baseline	5.70 (17.798)	25.00 (23.570)
		Min, Max change from baseline	-33.3, 33.3	8.3, 41.7
	Treatment discontinuation	n	30	38
		Mean (SD)	52.50(24.966)	65.35(21.879)
		Median	54.17	66.67
		Min, Max	0.0,83.3	16.7,100
		n change from baseline	30	37
		Mean (SD) change from baseline		
		Min, Max change from baseline	-83.3, 33.3	-50.0, 50.0
	Disease progression	n	32	43
		Mean (SD)	57.29(21.664)	72.09(20.484)
		Median	66.67	75.00
		Min, Max	16.7,83.3	25.0,100
		n change from baseline	30	42
		Mean (SD) change from baseline	-11.94(21.182)	-1.79 (18.177)
		Min, Max change from baseline	-58.3, 33.3	-41.7, 41.7

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; FAS, full analysis set; QoL, quality of life; SD, standard deviation.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	EGFR+ UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	EGFR+ UK is a patient driven charity established to provide information and support for EGFR mutation positive lung cancer patients, their families and loved ones. We are also dedicated to supporting research and advocacy, and are working to raise awareness of EGFR positive lung cancer and end the stigma associated with lung cancer in general. We currently have approximately 920 members, and are largely funded by fundraising activities, charitable donations, and some grants.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Patients share their experiences of treatment pathways and drug toleration on our private patient support forum, which is the main forum for the exchange of information and support. As we have approx. 920 members we are able to present a representative view of the experience of living with EGFR mutation positive lung cancer. We also ran two surveys with our membership exploring the experiences of EGFR+ patients in the UK in terms of their diagnosis, treatment, surveillance and wellbeing (*n*s for both were > 200). For this submission I have drawn on the experiences of our EGFR patient members, alongside my own personal experience.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	NSCLC with an EGFR mutation is a highly aggressive disease with significant physical, psychological, social, and economic consequences for patients and their families. EGFR-positive NSCLC disproportionately affects younger, non-smoking individuals, often women, who are likely to be working and may have dependent children. This diagnosis often comes as a profound shock, as one patient described: *"I was diagnosed at age 44 and felt very frightened, very alone, and completely overwhelmed. As a never-smoker, it was the last thing on my mind, and the shock and disbelief were very hard to cope with."* The disease places immense strain on both patients and their loved ones. Anxiety and depression are common, as illustrated by our annual survey of EGFR+ UK members (n=234), which showed that 1-in-3 of patients scored over the cut-off for diagnosable anxiety (using the GAD-7); and 1-in-4 showing likely clinical depression (using the PHQ-9). Both prevalence rates are significantly higher than that seen in the general population. Worrying about the future is common, with many reporting that uncertainty about how they will respond to treatment, fear about recurrence/progression, and ambiguity about future treatment options exacerbates the challenges of the disease, and reduces quality of life. Family dynamics and finances are often also affected, with normal activities like holidays and outings being disrupted or curtailed. Many of our members have young or school-aged children, whose lives are deeply impacted. Furthermore, EGFR patients often report experiencing a profound sense of loss and fear about the future: *"I feel robbed of my future—all those memories I may never have the chance to make, like my kids leaving school, going to university, getting married, starting a family."* Of the Stage 3 patients who responded to our annual survey, 50% underwent both chemo and radiation (either concurrently, or sequentially). For some, radical chemoradiation offers hope as a sites of disease are definitively treated with curative intent. However, relapse/progression rates are high, and recovery brings with it the fear of recurrence, which patients describe as a heavy psychological burden. One patient shared: *"While I know I have been lucky to have this radical treatment, it's difficult when you finish it and you are just left to get on with it. There is no safety net. I'm terrified, as I wasn't offered any type of maintenance treatment or anything, so I just feel like I am waiting for the other shoe to drop. Every scan I am waiting for bad news."* This lack of maintenance treatment is common, with half of the abovementioned Stage 3 chemoradiation patients reported being offered no maintenance therapy. In contrast, the other half received Osimertinib. The availability of Osimertinib as an option provides optimism, as it reduces the likelihood of recurrence and protects against brain metastases, which are common in EGFR-positive NSCLC. Furthermore, patients taking this drug

	report that it allows them to maintain a good quality of life with few side effects. One patient noted: *"Being on Osimertinib and having regular scans gives me invaluable reassurance. I feel like I'm doing something to keep my cancer at bay. So far so good and long may it stay that way."* In summary, NSCLC with an EGFR mutation profoundly affects patients and their families, creating challenges that extend beyond the physical disease. More effective treatment options are needed to provide hope and improve quality of life.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Chemoradiation for locally advanced disease is unlikely to 'cure' this disease and the high rate of recurrence calls for an additional step in the treatment path. At present, the current treatment pathway following chemoradiation seems to be "wait and watch". However, as described above, many patients find this incredibly stressful, and it significantly impacts their psychological wellbeing. Patients are often also aware of the high relapse/progression rates and feel that they want to be doing something else to prevent the cancer recurring. Additionally, EGFR+ NSCLC commonly metastasises to the brain, which is a source of great fear for many patients. Being off treatment completely increases the risk of symptomatic central nervous system (CNS) metastases developing.
8. Is there an unmet need for patients with this condition?	Yes. There is currently no agreed standard of care in relation to how a patient is treated following chemoradiation. This will result in some patients being disadvantaged and risking recurrence. One patient said: "Not doing anything feels like such a risk. It's really scary. I can't stop worrying about if or when it will come back." Other patients report feeling that it's unfair that some people seem to have been offered a maintenance drug following chemoradiation, but they haven't. This disparity in care (both within the UK, and in comparison to other countries) is both upsetting and frustrating to patients.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients are particularly positive about the fact that Osimertinib is a highly efficacious daily tablet taken at home, with few side effects – so having minimal impact on their day-to-day lives - but offers them protection against disease progression/recurrence. Osimertinib's convenience as an oral treatment is a significant advantage for maintenance treatment, allowing patients to spend more time with loved ones and maintain daily routines, allowing them to maintain a semblance of normalcy. The significant protection Osimertinib offers to both the body and the brain is also seen as a hugely beneficial, as it can reduce the risk of symptomatic central nervous system (CNS) metastases – which is a particularly common fear of EGFR patients.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There is some concern that if Osimertinib is prescribed as a maintenance drug, it may not be available as a later treatment or for re-challenge. TKI's have improved overall survival for patients who, by and large, learn to manage life whilst taking them. For some patients however there are significant side effects which can impact the patient's quality of life, most commonly rash, diarrhoea, paronychia and hair loss.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Some patients are very anxious about recurrence. Having an additional treatment that gives greater protection against recurrence is very reassuring to these patients.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The main issue is not so much with specific groups being disadvantaged, it is more about the equity of treatment quality and access across the UK. Differing regulations across the nations, and differing levels of expertise between (and even within) hospitals mean that patients often get a differing standard of care, depending on where they are treated. (I outlined the variations in care for Stage 3 EGFR patients above). That said, there are some notably underserved groups – for example, those in minority ethnic groups are less likely to engage with healthcare professionals and systems. Perhaps more could be done on translation of guidelines and research around treatment for these patient groups. Additionally, EGFR affects certain groups more than others (for example, it is more prevalent in women, and in Asian populations). Ensuring access to treatment and information about the treatment is relevant and understandable to these groups is essential.

Other issues

13. Are there any other issues that you would like the committee to consider?	While maintenance Osi is overwhelmingly seen as a positive option within the EGFR community, there are some concerns about the duration of treatment and monitoring plans. Patients worry about what will happen after the standard three-year treatment period: *"What will happen after three years when Osimertinib stops. Will the cancer come back? Will I still be scanned?"* They also worry about how taking this drug as a maintenance treatment will affect their treatment options further down the line.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Chemoradiation alone does not 'cure' this disease and the high rate of recurrence calls for an additional step in the treatment pathway. • Patient's greatest fear following treatment is recurrence. Maintenance Osimertinib gives patients more protection against recurrence. • Taking a daily TKI has minimal impact on the patient or their family and enables the patient to live a full and active life. • Patients need to understand how taking maintenance Osimertinib may impact their subsequent treatment options. • Continued use of Osimertinib after 3 years is not recommended. However, if after 3 years the patient continues to do well, removing Osimertinib seems harsh, unless it can be evidenced that the patient will not be disadvantaged by this action.

Thank you for your time.

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Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Patient Organisation Submission

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About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, work in lung cancer patient care (information, support and advocacy activity) and raise awareness of the disease and issues associated with it. Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	**RCLCF has received the following funding :** - Amgen (£30,000 for 1 year funding of Global Lung Cancer Coalition (GLCC) project) - BMS (£30,000 for 1 year funding of GLCC project; £1100 for Advisory board Honorarium) - Lilly (£30,000 for 1 year funding of GLCC project) - Boehringer Ingelheim (£30,000 for 1 year funding of GLCC project; £1820 Advisory board Honoraria) - Roche (1 year funding of GLCC project; £10,000 for Lung cancer Awareness Month initiative) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Novocure (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project) - Astra Zeneca (£30,000 for 1 year funding of GLCC project; £500 for Meeting Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker honorarium) - Regeneron (£30,000 for 1 year funding of GLCC project) - Gilead (£30,000 for 1 year funding of GLCC project; £460 speaker honorarium) - Merck (£30,000 for 1 year funding of GLCC project) - J &J (£20,000 for Lung Cancer Awareness Month initiative)
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, Patient Information Days, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The lung cancer patient population associated with this appraisal have locally advanced unresectable non small cell lung cancer and will have undergone platinum based chemoradiation. There is a high risk of recurrence or progression of lung cancer, which is of obvious concern to patients and their carers. Patients and their carers have continual anxiety that the lung cancer will progress. Symptoms of lung cancer, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. This group of patients are a very targeted group, having EGFR mutation positive lung cancer.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There is an obvious need for better treatments for this patient group to ensure therapies with better outcomes and fewer patients having progression of their lung cancer.
8. Is there an unmet need for patients with this condition?	Yes

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We note the study of Stage III unresectable EGFR mutated NSCLC, which randomly assigned patients without progression during or after chemoradiation to receive Osimertinib or placebo until disease progression or the regimen discontinued. The percentage of patients who were alive and progression free at 12 months was 74% with Osimertinib and 22% with placebo. Interim Overall Survival showed 36 month overall survival among 84% of the Osimertinib arm and 74% with placebo. Osimertinib is an oral therapy, which has been widely used over recent years.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The addition of Osimertinib treatment and the side effects associated with it.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This indication is for the highly selected group of patients with EGFR mutation positive lung cancer.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Highly selected group of patients • Clinical trial shows a significant and meaning improvement in disease free survival in this patient group.

Thank you for your time.

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Professional organisation submission

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of Respiratory Nurses (ARNS) was established in 1997 as a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve progression free survival, improve life expectancy, improve quality of life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in progression free survival. Ongoing reduction in tumour burden or no evidence of progression on treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, lung cancer remains difficult to treat. All avenues of second line treatments should be explored to improve patient survival. Maintenance treatment avenues should be explored.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Treated with Durvalumab after chemorad currently.
9a. Are any clinical guidelines used in the	Guidance 798, 122, 9

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes currently well defined pathway for first line treatment with chemoradiation. Some variation in treatment for second line depending on previous experience of oncologist.
9c. What impact would the technology have on the current pathway of care?	Improve maintenance treatment options.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used in the same was Durvalumab is currently used.
10a. How does healthcare resource use differ between the technology and current care?	Additional / alternative line of treatment
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Oncology clinics only
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of oncology nurses to administer the drug. Education to oncologists and pharmacists to understand the regime and protocol. Resource in pharmacy to produce the correct drug mix for patients.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	May depend on recovery from chemo rad – need to be well enough to continue with maintenance treatment.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Should be comparable to administering current medications, will involve additional trips to hospital and additional appts in chemo clinics.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	EGFR mutation status needs to be assessed.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Progression free survival may also bring increased quality of life.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes

16b. Does the use of the technology address any particular unmet need of the patient population?	Provide an alternative to Durvalumab
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects can be managed but need careful monitoring. Can be distressing to patients.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Life expectancy, progression free survival, quality of life
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical	Not to my knowledge

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA798]?	No
21. How do data on real-world experience compare with the trial data?	n/a

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No

Topic-specific questions

23. In your experience and acknowledging that there is evidence to suggest it is inappropriate, is there much use of durvalumab maintenance after concurrent chemoradiation for EGFR positive NSCLC in NHS practice? **If so, would you be able to comment on numbers or proportions having this treatment?**	Have seen some patients who have had Durvalumab post chemorad with good progression free survival, but this is often the case after chemorad anyway so difficult to know if it is making a difference.
24. Do you consider osimertinib maintenance after chemoradiation to be a curative treatment? **Are you able to comment on the numbers or proportions of people who might be considered cured after having active monitoring subsequent to chemoradiation?**	Chemoradiation is a curative intent treatment alone, Osimertinib may not be required.

25. Do you consider there to be any subgroups which might have a different response to osimertinib maintenance after chemoradiation?	Those included with EGFR mutations

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.	• Maintenance treatment for patients after chemorad should be considered • Must be aware that some patients may not be eligible as performance status can be reduced after chemorad. • • •

Thank you for your time.

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Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic Oncology Group (BTOG)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. Funded by sponsorship and registration fees.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	BTOG 2024 Platinum Sponsorship £30,000
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment for combined chemotherapy and radiation in this stage of disease is an attempt at cure. The placebo arm of LAURA suggest that in the population of lung cancer with EGFR mutations this is rarely achieved at present. If cure cannot be achieved then prolongation of time where patient does not have recurrent disease and associated symptoms should be the primary aim along with maintaining associated related quality life and ability to operate within society.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	I would consider all the below endpoint as potentially clinically meaningful An improvement in median progression free survival by six months An increase in patients who are progression free at three years by 10% An increase in patients who are progression free at five years by 5% An increase in median overall survival by six months; An increase inpatient who are alive at three years by 5%
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes Despite the administration of chemotherapy and radiotherapy at high doses with the intention of cure in the placebo arm, the vast majority of patients relapsed within the first two years of treatment at which point they would be receiving further treatment with palliative intent.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	At present time patients will receive chemotherapy and radiotherapy together as administered within the clinical trial. Some patients may then receive a year of durvalumab if their tumours express PDL1 one. However, the benefits in this situation are uncertain and there is concern in the community about the impact on downstream treatments

	such as Osimertinib if the downstream setting (with a potential increase in pneumonitis rates) so it is increasingly not given.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes the European Society of Medical Oncology guidelines on Oncogene driven lung cancer are commonly used. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up Hendriks, L.E. et al. Annals of Oncology, Volume 34, Issue 4, 339 - 357
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There are some variations in the pathway. There are differences in the radiotherapy dosing strategies used. Most centres even use 60Gy in 30 fractions (over 6 weeks) or 55Gy in 20 fractions (over 4 weeks) There are also differences in the Chemotherapy used. Some centres will use cycles of chemotherapy either before or after the concurrent chemo-radiotherapy. In general platinum doublet based chemotherapy is used but there are variations in whether it is carboplatin or cisplatin and the exact schedule used. There are also differences in the partner chemotherapy, most commonly used partners include vinorelbine and paclitaxel. As described above, there are variations in the use of durvalumab, but in general expert opinion is that this should no longer be used in this population. There are also variations in follow-up. In some centres patients will be followed up by respiratory physicians, in others by oncology services. There will also be variation in how often patients are scanned and what imaging modalities are used.
9c. What impact would the technology have on the current pathway of care?	It would replace surveillance in suitable patients. In those patients who presently get chemotherapy after concurrent chemotherapy or durvalumab it would replace that.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. Osimertinib is already routinely used in the palliative setting and as adjuvant treatment following surgery within the NHS.
10a. How does healthcare resource use differ	Patients would be seen monthly to 2 monthly in Oncology clinics for administration of treatment whilst on Osimertinib. They may be scanned more frequently on Osimertinib than on present follow-up pathways.

between the technology and current care?	Given the delay in recurrence there would be an associated delay or reduction in the cost of management of metastatic disease and it associated complications ; most of these patients will start eventually start osimertinib on the diagnosis of metastatic disease in the present pathway.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Oncology centres
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. Already routinely used in other settings.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the clinical data from Laura suggest a pronounced improvement in progression free survival with most patients on placebo relapsing within two years. Whether this translates to overall survival has yet to be seen but has been observed in other settings where adjuvant Osimertinib has been used and for example following Surgery in earlier stage disease
11a. Do you expect the technology to increase length of life more than current care?	Possibly. See comment above. Presently some uncertainty about this. I suspect there will be some survival benefit but the size is presently unknow n
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. Relapse is often associated with significant symptoms including those due to the frequent occurrence of brain metastases in this population; with its subsequent impact not only physical function but significant psychosocial effect.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	I do not think so. Osimertinib is relatively easy to administer and given routinely to a significant number of patients in lung cancer clinics in the NHS.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No. Patients will be treated until progression as was performed in the clinical trial. This will require regular CT surveillance.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	No. The treatment is routinely already used in the metastatic setting and as adjuvant treatment following surgery. It will be the first targeted treatment available following curative chemotherapy and radiotherapy across cancer types with the aim of improving progression free and hopefully overall survival.
16a. Is the technology a 'step-change' in the management of the condition?	Yes given the poor outcomes in the placebo arm and the marked benefit of treatment in progression free survival I do believe this it should be regarded as a step change.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes. At present time many of these patients believe they are receiving curative type treatment. In reality it is London likely that this is the case and that most of them will relapse in a very short period of time.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In general, this is a well tolerated agent with a good side-effect profile, with minimal deductions and discontinuations due to adverse events.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival, Progression free survival and health related quality of life all measured within the study
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Relationships of progression free survival and overall survival are not always clear. In general in this context progression free survival benefit does predict overall survival benefit.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA798]?	No
21. How do data on real-world experience	No good real world data sources in the UK. Appears to be in keeping with real world experience.

compare with the trial data?	

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A

Topic-specific questions

23. In your experience and acknowledging that there is evidence to suggest it is inappropriate, is there much use of durvalumab maintenance after concurrent chemoradiation for EGFR positive NSCLC in NHS practice? **If so, would you be able to comment on numbers or proportions having this treatment?**	Yes, I think there will be patients in this population presently receiving durvalumab, Although there is emerging evidence that this is not effective but may be potentially harmful; not only due to the side-effects of durvalumab, but also an increased risk of toxicity when patients do move onto Osimertinib with an increased incidence of pneumonitis if given shortly after durvalumab (within 6 months of completion). The number will vary with centre and experience leading to inequity in care. Our centre stopped recommending this treatment in this population 2- 3 years ago, but I know that there are centres who may still give. This may be 15 to 20% of the population in England.
24. Do you consider osimertinib maintenance after chemoradiation to be a curative treatment? **Are you able to comment on the numbers or proportions of people who might be considered cured after having active monitoring subsequent to chemoradiation?**	I think this is difficult to say. I suspect in the vast majority of patients it is not curative but there may be a small number of patients where is able to eradicate any micro metastatic disease with the aid of the body's immune system and this could lead to cure. This would be supported by the survival benefit that has been observed with adjuvant Osimertinib in the post surgery setting, accepting this is earlier stage disease. Normally we would suggest that approximately 20% of patients receiving concurrent chemo radiotherapy for lung cancer would be cured by this treatment with active monitoring alone. I think the emerging data suggest that this will be lower for patients with EGFR mutant lung cancer and this would be supported by

	the placebo arm in LAURA.
25. Do you consider there to be any subgroups which might have a different response to osimertinib maintenance after chemoradiation?	No.

Key messages

26. In up to 5 bullet points, please summarise the key messages of your submission.	• Significant unmet medical need with most patients relapsing shortly after what is hoped to be curative treatment • Will be easy to bring into routine practice given already used in other settings in the NHS • Impact on survival uncertain at present given these patients would access osimertinib in the metastatic setting • Will reduce inappropriate durvalumab use in this population •

Thank you for your time.

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Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **12th June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation, and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Elizabeth Toy
2. Name of organisation	Royal Devon University Healthcare NHS Foundation Trust
3. Job title or position	Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer? ☐ A specialist in the clinical evidence base for EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer or the technology (osimertinib)? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)

organisation's submission)	
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation? (For example, to stop progression, to	To reduce the risk of recurrent/ progressive cancer and eliminate micro metastases and to extend both progression free and overall survival

improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Extension of progression free survival by > six months An improvement >/= 5% improvement in the probability of disease free survival A reduction of >/= 5 % in the risk of developing brain metastases
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation?	Yes- the Laura Trial demonstrates that patients with EGFR driven cancers have poor outcomes from conventional chemoradiation alone (inferior to outcomes in comparison to non EGFR mutation driven tumours) Recurrent disease has a devastating effect on both patients and their families.
11. How is EGFR mutation-positive	Lung Cancer services in England are commissioned to be delivered using the Optimal Lung cancer Pathway and follow NICE Guidance (NG122) which recommends concurrent chemoradiation for locally advanced cancers but also reflects more recent advances made and

locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	availability of drugs through the Cancer Drugs Fund (CDF) and other technology appraisals e.g. Durvalumab for the maintenance treatment of unresectable NSCLC after platinum based chemoradiation. (TA798) Clinical Oncologists also practice in line with the RCR Lung Cancer Consensus Statements- these do not consider EGFR Positive Cancers differently to any other type of NSCLC. The majority of Thoracic Clinical Oncologists (but not all) would not however add Maintenance Durvalumab following chemoradiation as although there were a small number of patients within the PACIFIC Study who were EGFR positive- evolving consensus is that patients with EGFR mutation driven cancers derive little benefit from immunotherapy. Were Osimertinb be funded post chemoradiation I think the use of Durvalumab in this indication would cease completely. I believe there would be widespread/ uniform uptake of Osimertinib following chemoradiation for suitable patients. This group of patients would therefore be less likely to be rechallenged with Osimertinib should they relapse.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The Oncology community are very experienced in the use of Osimertinib in both the adjuvant and metastatic setting The technology should be used in a specialist oncology clinic with overall responsibility for care being provided by a medical or clinical oncologist specialising in thoracic oncology. The additional workload will require more appointments for the service to monitor treatment, manage toxicities and ensure clinical benefit. There are several services who use non-medical prescribers to provide many of these appointments however there is a training requirement for them to gain expertise with this class of systemic therapy. There is a recognised shortage in England of oncologists, specialist nurses and specialist pharmacists however the number of patients suitable for this treatment is relatively small per MDT compared to patients with more advanced metastatic disease receiving the same drug. I do not therefore see this being a barrier to implementation. There will also be a small increase in pharmacy dispensing resource and radiology resource required. This should be balanced against the reduced requirement for services for patients who would have relapsed had they not received treatment.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes the results from the LAURA trial show highly clinically significant improvements in disease free survival and a reduction in intracranial disease. This represents a significant breakthrough in the patient care. Although there may be a small reduction in health related quality of life due to the potential toxicities from the technology this will be offset by the longer term gains of improved progression free survival and freedom from disease. There is a significant adverse impact on quality of life at the point of cancer recurrence following chemoradiation..
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment is only appropriate for patients whose tumour exhibits an activating EGFR mutation, this is a small proportion of the general lung cancer population. Dependant on geographic region between 7 and 15% of NSCLC will harbour an EGFR mutation. Although radiation pneumonitis usually occurs at 8-12 weeks post chemoradiation- if a patient were to develop this to a significant degree prior to commencing Osimertinib this may be considered a relative contra-indication.
15. Will the technology be easier or more difficult to use for	Oncology services are very experienced in the management of patients receiving Osimertinib for stage IV NSCLC and in the adjuvant setting following surgery. I do not anticipate other than a small increase in the number of patients accessing clinics, blood test and ECG monitoring in addition to follow up imaging, there to be any barriers to adoption.

patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The criteria for starting treatment would be in line with the clinical trial eligibility for the LAURA study. Treatment would continue indefinitely unless the patient was to develop recurrent disease, unacceptable toxicity, a significant concomitant illness or patient choice to stop.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	Increasing progression free survival will have a positive impact on those connected to the patient.

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact	Given the highly targeted nature of the technology which has low levels of toxicity I believe this represents a step change in the management of this very specific group of patients where there is an unmet need. Conventional chemoradiotherapy outcomes are extremely poor in this group of patients. The technology will reduce both risk of distant relapse and local progression. These statistically significant and clinically meaningful improved long term outcomes will have a very positive effect on health related benefits. It will, for the majority of patients receiving treatment , keep them well for longer and offer a chance of a longer life span.

on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Osimertinib has been widely used in the palliative setting and following radical surgery. It is generally very well tolerated with the vast majority of toxicity being Grade 1 or 2 and easily managed with supportive medicines or with dose reductions. The side effect profile of Osimertinib is generally favourable when compared to immunotherapy..
20. Do the clinical trials on the	The trial comparator arm mirrors standard practice in England, Osimertinib is not currently available for use in this patient population.

technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to	Overall survival, Progression free survival and intracranial relapse free survival are the most important outcomes(providing toxicity of the intervention is manageable) and all were measured within the LAURA trial. The overall survival data remains immature due to high rates of crossover although there is a favourable trend to improvement. I am unaware of any additional adverse effects.

light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	I am unaware of any published real-world data.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this	No- all patients in this group should have access to appropriate genomic testing funded by the NHS as part of their work up for radical treatment

condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and	

equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Osimertinib is well tolerated and has a convenient dosing schedule.

Osimertinib offers clinically meaningful protection against brain metastases.

Maintenance Osimertinib significantly extends progression free survival which is vital for this patient population additionally there is a favourable trend for an improvement in overall survival

The overall treatment should be supervised by a Medical or Clinical Oncologist but clinical monitoring and patient support may be delivered by a non-medical prescriber.

Maintenance Osimertinib should be recommended for use in the treatment of EGFR mutation positive NSCLC following chemoradiation

Thank you for your time.

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Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer or caring for a patient with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Thursday 12th June 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Patient expert statement

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation

Table 1 About you, EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation, current treatments and equality

1. Your name	Shanta (Nina) Kale
2. Are you (please tick all that apply)	☒ A patient with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	EGFR+ UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation? **If you are a carer (for someone with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation) please share your experience of caring for them**	I was a very healthy individual who was diagnosed in 2018 September, In Canada , Ottawa. I refused to believe I could have cancer for nearly 10 days. When I realized I decided I will control the disease and not the other way round. I was put on Osimertinib with many side effects but the dreaded unpredictable, vicious diarrhoea was the worst. Right from the beginning I had it and it completely drained me. Over the years Tagrisso gave me second chance to live and am eternally grateful for that. I got to spend time with my loved ones and see my two precious grandkids who arrived later.The diarrhoea was worse over the years. Slowly I started loosing confidence in myself, got irritated very easily, anxious and stopped socializing as the diarrhoea could happen anywhere and anytime for any reason. I had radiation and chemo at the same time a year later. I retired and moved back to the UK. My scans were stable over the years. My dosage of Tagrisso was reduced to 40 and I got relief from diarrhoea and the other side effects also were ok. I started nearly leading a normal life. And had completed 6 years and was thinking that "C" has gone from my life when last year I had progression. The mutation was the same . I had cryoablation at the Brompton. I was put back on Tagrisso 80mg and the diarrhoea returned so it was reduced back to 40 mg. Life is again scan to scan with enormous scanxiety.
7a. What do you think of the current treatments and care available for EGFR mutation-positive locally	I am not aware of any medication after Tagrisso for my mutation. I had read about one but I think its not available un the UK. There are adjuvant therapies . People in

advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	my support group have had cyberknife treatment but my brain scans are clear so thank God I haven't thought about it. Immunotherapy again is not for me. People from my group who have progressed go on in to clinical trials but I have no experience of that either.
8. If there are disadvantages for patients of current NHS treatments for EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Sorry I do not know about these. I feel that lot of research has been done an lot of medications are in the market which are not available on NHS.
9a. If there are advantages of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I have not had any other treatments other than targeted therapy, chemo radiation so I unfortunately can't reply.
10. If there are disadvantages of EGFR mutation-positive locally advanced unresectable non-small-cell	I can reply to what I don't know so cant comment

lung cancer after platinum-based chemoradiation over current treatments on the NHS please describe these. For example, are there any risks with EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Sorry can't comment
12. Are there any potential equality issues that should be taken into account when considering EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation and EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	I don't think the "C" chooses religion, race, age, gender when it strikes. When I was diagnosed I was a healthy, non smoking (didn't have anyone in the family smoking too) person living in one of the cleanest (air quality wise) places on earth. my genes decided to mutate and I am here.

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	There is treatment and no cure. With the world progressing as it is and lot of research going in we need more medicines. I also feel these should be available world wide at reasonable rates The stigma to lung cancer has to go . More awareness . The cancer patient instead of feeling guilty as they do so as I have experienced in my support group here and in Canada where I did support work too should consider it as a chronic condition like diabetes and take medications and think positively rather that shun yourself and feel depressed. Yes we are going through a lot of pain and worry and anxiety but I personally don't think there is any need to have the family , friends who care for you and love you go through it as well. Think positive . Que sera sera.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is treatment no cure
- Its just an illness no stigma
- After recurrence what?? New lines of treatment
- Need more awareness
- We need understanding not sympathy

Thank you for your time.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR172246

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CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

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Samuel Bryning	Critical appraisal of the economic evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Vincy Huang	Critical appraisal of the economic evidence
James Mahon	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the search strategies
Joanne McEntee	Critical appraisal of the company submission
Lynn Campbell	Clinical advice and critical appraisal of the clinical evidence

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AE	adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BICR	blinded independent central review
BSA	body surface area
BSC	best supportive care
CAA	Commercial Access Agreement
CCRT	concurrent chemoradiation
CFB	change from baseline
CI	confidence interval
CNS	central nervous system
CRT	chemoradiation
CS	company submission
CSR	clinical study report
DCO	data cut-off
DFS	disease-free survival
DSA	deterministic sensitivity analysis
EAG	Evidence Assessment Group
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth-factor receptor mutation
EGFR-TKI	epidermal growth-factor receptor tyrosine kinase inhibitor
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire lung cancer module
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
HCRU	healthcare resource use
HR	hazard ratio
HRQoL	health-related quality of life
HSUV	health state utility value
HTA	Health Technology Assessment
ICER	incremental cost effectiveness ratio
K-M	Kaplan-Meier
MMRM	mixed-effect model for repeated measures
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme

PD	progressed disease
PD-L1	programmed cell death-ligand 1
PF	progression-free
PFS	progression-free survival
PFS2	second progression-free survival
PPS	post-progression survival
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
QD	once daily
SCRT	subsequent chemoradiation
SLR	systematic literature review
TFST	time to first subsequent therapy
TKI	tyrosine kinase inhibitor
TSST	time to second subsequent therapy
TTD	time to treatment discontinuation
TTDM	time to death or distant metastases
TTP	time to progression
VAS	visual analogue scale
WHO PS	World Health Organisation performance status

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Section 1.3 to Section 1.6 explain the key issues identified by the EAG in more detail. Key cost effectiveness results are presented in Section 1.7.

All issues identified represent the EAG's view, not the opinion of National Institute of Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table A Summary of the EAG's key issues

Issue	Summary of issue	Report sections
Issue 1	Limitations of the osimertinib clinical effectiveness evidence	2.4.2, 3.2.3, 3.6
Issue 2	Representativeness of LAURA trial placebo arm results	3.3, 3.3.1, 3.6
Issue 3	Unclear long-term impact of treatment with osimertinib on OS	3.3, 3.3.1, 3.6
Issue 4	Post-progression survival for patients initially treated with BSC	6.2.1
Issue 5	Osimertinib time to treatment discontinuation	6.4
Issue 6	Proportion of patients receiving subsequent treatment	6.5
Issue 7	Company model health state utility values	6.6
Issue 8	Post-progression survival for patients initially treated with osimertinib	6.2.2
Issue 9	Time to progression and progression-free survival for patients treated with osimertinib	6.3

BSC=best supportive care; EAG=External Assessment Group; OS=overall survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER per QALY gained is the ratio of the extra cost for every QALY gained.

The company model generates cost effectiveness results for the comparison of osimertinib versus best supportive care (BSC). The EAG revisions that have the biggest effect on company costs and QALYs are:

- using the Weibull distribution used to generate post-progression survival (PPS) estimates for patients initially treated with BSC
- using the same distribution to generate osimertinib progression-free survival (PFS) and time to treatment discontinuation (TTD) estimates from the start of the model time horizon
- removal of the 10-year osimertinib treatment stopping rule.

The EAG also explored the impact on costs and QALYs of the following changes:

- using the exponential distribution to generate PPS estimates for patients treated with osimertinib
- using the exponential distribution to generate time to progression (TTP) and PFS estimates for patients treated with osimertinib.

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Limitations of the osimertinib clinical effectiveness evidence

Report section	2.4.2, 3.2.3, 3.6
Description of issue and why the EAG has identified it as important	Clinical advice to the EAG is that, overall, the baseline characteristics of the LAURA trial patients are representative of NHS patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT. However, compared to NHS patients: • a higher proportion of LAURA trial patients were Asian • no LAURA trial patients were black. Clinical advice to the EAG is that the clinical effectiveness of osimertinib is unlikely to be affected by ethnicity. The Asian subgroup PFS HR was 0.20 (95% CI: 0.13 to 0.29) whereas the non-Asian subgroup PFS HR was 0.48 (95% CI: 0.20 to 1.19); however, the non-Asian subgroup only included a very small number of patients and the number of events was low (non-Asian osimertinib patients: n=14/27; non-Asian placebo patients: n=8/11) and therefore it is difficult to draw conclusions about the PFS treatment effect for patients in this subgroup.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Not known.
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opinion to determine whether LAURA trial results can be generalised to NHS patients.

CI=confidence interval; CRT=chemoradiation; EAG=External Assessment Group; EGFRm=epidermal growth factor receptor mutation; HR=hazard ratio; NSCLC=non-small cell lung cancer; NHS=National Health Service; PFS=progression-free survival

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 2 Representativeness of LAURA trial placebo arm results

Report section	3.3, 3.3.1, 3.6
Description of issue and why the EAG has identified it as important	Clinical advice to the company was that LAURA trial placebo arm results were "poor" compared to results expected in NHS clinical practice; clinical advice to the EAG is that outcomes for NHS patients with EGFRm-positive locally advanced unresectable NSCLC following CRT are uncertain. The company identified six studies that reported PFS for patients with EGFRm-positive locally advanced unresectable NSCLC following CRT. The LAURA trial placebo arm median PFS was lower than the median PFS reported in the identified studies.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	If the LAURA trial placebo arm median PFS is lower than the expected PFS for NHS patients treated with BSC then the ICER per QALY gained for osimertinib versus BSC may be underestimated.
What additional evidence or analyses might help to resolve this key issue?	Seek further clinical opinion of whether LAURA trial placebo arm results can be generalised to NHS patients treated with BSC.

BSC=best supportive care; CRT=chemoradiation; EAG=External Assessment Group; EGFRm=epidermal growth factor receptor mutation; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; NSCLC=non-small cell lung cancer; NHS=National Health Service; PFS=progression-free survival

Issue 3 Unclear long-term impact of treatment with osimertinib on OS

Report section	3.3, 3.3.1, 3.6
Description of issue and why the EAG has identified it as important	Compared with placebo, maintenance treatment with osimertinib numerically improved OS. The EAG considers that it is currently difficult to draw conclusion about the osimertinib OS treatment effect as data are immature (at the time of the 5 January 2024 DCO, the LAURA trial OS data were only 19.9% mature) and 50/62 (80.6%) LAURA trial placebo patients received osimertinib after first progression.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost effectiveness estimates?	Not known.
What additional evidence or analyses might help to resolve this key issue?	The final OS analysis will be conducted when the data are approximately 60% mature; this is currently anticipated to be [redacted]. Seek clinical opinion on the long-term impact of treatment with osimertinib on OS.

DCO=data cut-off; EAG=External Assessment Group; OS=overall survival

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 4 Post-progression survival for patients initially treated with BSC

Report section	6.2.1
Description of issue and why the EAG has identified it as important	At the time of the 5 January 2024 DCO, LAURA trial placebo arm PPS data were only 21% mature and 50/62 (80.6%) of patients had received osimertinib as their first subsequent treatment. In the company model, mean survival in the PD health state for patients initially treated with BSC who receive osimertinib as their first subsequent treatment is substantially lower than the expected survival of patients treated with osimertinib as a first-line treatment in the metastatic setting (TA654).
What alternative approach has the EAG suggested?	Use the Weibull distribution to generate PPS estimates for patients initially treated with BSC.
What is the expected effect on the cost effectiveness estimates?	The deterministic ICER per QALY gained increases to £38,360 (an increase of £19,270).
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion on the expected PPS of patients initially treated with BSC.

BSC=best supportive care; DCO=data cut-off; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PD=progressed disease; PPS=post-progression survival; QALY=quality adjusted life year

Issue 5 Osimertinib time to treatment discontinuation

Report section	6.4
Description of issue and why the EAG has identified it as important	The company generated osimertinib TTD estimates using LAURA trial K-M data up to 36 months and an exponential distribution thereafter. The sustained separation of the PFS and TTD curves after 36 months is not supported by LAURA trial PFS and TTD K-M data. The company assumed that no patients would remain on treatment with osimertinib after 10 years; a treatment stopping rule is not included in the osimertinib expected licence or the LAURA trial protocol.
What alternative approach has the EAG suggested?	i) Use the same distribution to generate osimertinib PFS and TTD estimates from the start of the model time horizon. ii) Remove the 10-year osimertinib treatment stopping rule.
What is the expected effect on the cost effectiveness estimates?	i) The deterministic ICER per QALY gained increases to £24,628 (an increase of £5,538). ii) The deterministic ICER per QALY gained increases to £23,519 (an increase of £4,429).
What additional evidence or analyses might help to resolve this key issue?	None.

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Issue 6 Proportion of patients receiving subsequent treatment

Report section	6.5
Description of issue and why the EAG has identified it as important	In the company model, i) the proportion of patients who received at least one subsequent treatment and ii) the proportion who received osimertinib as a first subsequent treatment were based on the average of clinical expert estimates. These estimates are lower than observed in the LAURA trial.
What alternative approach has the EAG suggested?	Use estimates informed by LAURA trial data so that modelled costs and post-progression survival are aligned.
What is the expected effect on the cost effectiveness estimates?	The deterministic ICER per QALY gained decreases to £16,543 (a decrease of £2,547).
What additional evidence or analyses might help to resolve this key issue?	None.

EAG=External Assessment Group; ICER= incremental cost effectiveness ratio; QALY=quality adjusted life year

Issue 7 Company model health state utility values

Report section	6.6
Description of issue and why the EAG has identified it as important	The company PF utility value exceeds the general population utility value (age- and sex- matched to LAURA trial baseline characteristics). The company PD utility value does not reflect the decline in HRQoL that occurs as disease progresses.
What alternative approach has the EAG suggested?	i) Set the PF utility value to the age- and sex-matched general population utility value. ii) Set the PD utility value to the average of the TA654 PFS and PD utility values.
What is the expected effect on the cost effectiveness estimates?	i) The deterministic ICER per QALY gained increases to £20,999 (an increase of £1,909). ii) The deterministic ICER per QALY gained decreases to £17,999 (a decrease of £1,090).
What additional evidence or analyses might help to resolve this key issue?	None.

EAG=External Assessment Group; HRQoL=health related quality of life; ICER=incremental cost effectiveness ratio; PD=progressed disease; PF=progression-free; PFS=progression-free survival; QALY=quality adjusted life year

1.6 Other key cost effectiveness issues: EAG exploratory analyses

Issue 8 Post-progression survival for patients initially treated with osimertinib

Report section	6.2, 6.2.2
Description of issue and why the EAG has identified it as important	LAURA trial osimertinib arm PPS follow-up was short and few patients were at risk of post-progression death. PPS for patients initially treated with osimertinib may be underestimated.
What alternative approach has the EAG suggested?	Use the exponential distribution to generate PPS estimates for patients treated with osimertinib
What is the expected effect on the cost-effectiveness estimates?	The deterministic ICER per QALY gained decreases to £16,477 (a decrease of £2,613)
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion as to the expected PPS of patients initially treated with osimertinib

EAG=External Assessment Group; ICER= incremental cost effectiveness ratio; PPS=post-progression survival; QALY=quality adjusted life year

Issue 9 Time to progression and progression-free survival for patients treated with osimertinib

Report section	6.3
Description of issue and why the EAG has identified it as important	The company selected the Weibull distribution to generate TTP and PFS estimates for patients treated with osimertinib. It is uncertain whether the hazard of progression implied by the Weibull distribution represents the change in hazard observed in the LAURA trial osimertinib arm and produces clinically plausible long-term PFS estimates.
What alternative approach has the EAG suggested?	Use the exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib
What is the expected effect on the cost-effectiveness estimates?	The deterministic ICER per QALY gained increases to £25,611 (an increase of £6,521)
What additional evidence or analyses might help to resolve this key issue?	Seek clinical opinion as to which distribution produces the most clinically plausible hazard of progression and long-term PFS estimates.

EAG=External Assessment Group; ICER= incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year; TTP=time to progression

1.7 Summary of EAG's alternative ICERs per QALY gained

Minor modelling errors identified and corrected by the EAG are described in Section 6.1. Summary deterministic and probabilistic cost effectiveness results are presented in Table B and Table C. For further details of the revisions and exploratory analyses carried out by the EAG, see Section 6.7.

Table B Deterministic results (osimertinib PAS and CAA prices)

Scenario/EAG revisions	Incremental		ICER (£/QALY)	Change from A2
	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	**£19,225**	**-**
A2. EAG corrected company clarification base case	[redacted]	[redacted]	**£19,090**	**-**
R1) Weibull distribution to generate PPS estimates for patients receiving BSC	[redacted]	[redacted]	£38,360	£19,270
R2) Osimertinib TTD estimates generated using the same distribution selected for PFS	[redacted]	[redacted]	£24,628	£5,538
R3) Removal of 10-year osimertinib treatment stopping rule	[redacted]	[redacted]	£23,519	£4,429
R4) Subsequent treatment proportions informed by LAURA trial	[redacted]	[redacted]	£16,543	-£2,547
R5) Set PF utility value to age and sex-matched general population utility value	[redacted]	[redacted]	£20,999	£1,909
R6) PD value: average of TA654 HSUVs	[redacted]	[redacted]	£17,999	-£1,090
B. EAG alternative base case	[redacted]	[redacted]	**£68,602**	**£49,512**
S1) Exponential distribution to generate PPS estimates for patients treated with osimertinib	[redacted]	[redacted]	£16,477	-£2,613
S2) Exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib	[redacted]	[redacted]	£25,611	£6,521
C1. B+S1	[redacted]	[redacted]	**£48,444**	**£29,354**
C2. B+S1+S2	[redacted]	[redacted]	**£50,291**	**£31,201**

BSC=best supportive care; CAA=Commercial Access Agreement; EAG=External Assessment Group; HSUV=health state utility value; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PD=progressed disease; PF=progression-free; PFS=progression-free survival; PPS=post-progression survival; QALYs=quality adjusted life year; TTD=time to treatment discontinuation; TTP=time to progression

Table C Probabilistic results (osimertinib PAS and CAA prices)

Scenario/EAG revisions	Incremental		ICER (£/QALY)	Change from A2
	Cost	QALYs		
A1. Company clarification base case	[redacted]	[redacted]	**£17,878**	**-**
A2. EAG corrected company clarification base case	[redacted]	[redacted]	**£18,940**	**-**
B. EAG alternative base case	[redacted]	[redacted]	**£64,239**	**£45,299**

CAA=Commercial Access Agreement; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal focuses on osimertinib for the maintenance treatment of epidermal growth factor receptor mutation (EGFRm)-positive locally advanced unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed during or following platinum-based chemoradiation (CRT).

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. Additional evidence was provided by the company during the clarification stage.

2.2 Background

2.2.1 Non-small cell lung cancer (NSCLC)

Lung cancer is the third most common cancer in the UK;[1] approximately 49,200 people are diagnosed with lung cancer each year.[1] Lung cancer is the most common cause of cancer-related death in England;[2] in 2017, the age standardised mortality rate for women and men with lung cancer was 46.1 per 100,000 and 65.8 per 100,000, respectively.[2]

Lung cancer is categorised into NSCLC, which accounts for around 80% to 85% of all lung cancer cases in England, and small cell lung cancer.[3] NSCLC is further categorised into two main histological types: non-squamous type carcinomas and squamous type carcinomas.[4] Non-squamous type carcinoma represents around 70% of all NSCLC cases and can be divided into two main histological subtypes: adenocarcinoma and large cell carcinoma.[4]

2.2.2 EGFRm-positive NSCLC

NSCLC can be further classified by testing for genetic markers that have been identified as oncogenic drivers; these include EGFR mutations.[5] Approximately 10% of patients with NSCLC have EGFRm-positive disease.[6] EGFR mutations most commonly occur in adenocarcinomas.[7]

2.2.3 Osimertinib

Osimertinib is a third-generation tyrosine kinase inhibitor (TKI).[8] Osimertinib is an irreversible inhibitor of epidermal growth factor receptors (EGFRs) with sensitising- or resistance-mutations and prevents downstream signalling to stop tumour growth and promote cell cycle arrest.[8]

Osimertinib is administered orally and is available as 40mg and 80mg tablets.[9] The recommended dose for patients with EGFRm-positive locally advanced unresectable NSCLC after CRT is 80mg osimertinib once a day (QD).[9]

If patients are unable to tolerate 80mg osimertinib QD, it is recommended that the dose is reduced to 40mg QD.[10] Dose interruptions until recovery are recommended for patients who experience Grade 2 radiation pneumonitis, QTc interval >500msec on at least 2 separate electrocardiograms (ECGs) or any Grade ≥3 adverse events (AEs).[10] Treatment discontinuation is recommended for patients who experience Grade ≥3 radiation pneumonitis, QTc interval prolongation with signs of serious arrhythmia, Stevens-Johnson syndrome and toxic epidermal necrolysis, aplastic anaemia or any Grade ≥3 AE that does not improve after a ≤3 week dose interruption.[9]

Osimertinib is not yet licensed in the UK as a maintenance treatment option for patients with EGFRm-positive locally advanced unresectable NSCLC whose disease has not progressed during or after CRT. European Medicines Agency (EMA) approval[11] was received in December 2024 and UK Medicines and Healthcare products Regulatory Agency (MHRA) approval is expected in May 2025 (CS, Table 2). The anticipated UK licensed indication is "for the 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" (CS, Table 2).

Clinical advice to EAG is that in current National Health Service (NHS) clinical practice, upon disease progression after CRT, patients with EGFRm-positive locally advanced unresectable NSCLC are treated with osimertinib.

2.3 Company's overview of current service provision

The company has presented the current NHS treatment pathway for patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT and the positioning of osimertinib should osimertinib be recommended by National Institute of Health and Care Excellence (NICE) for routine commissioning (CS, Figure 2).

The company has positioned (CS, Figure 2) treatment with osimertinib as an alternative to best supportive care (BSC). Osimertinib is intended to be used as a maintenance therapy to prevent disease progression after CRT. Clinical advice to the company[12] is that BSC consists of active monitoring only. Clinical advice to the EAG is that BSC consists of active monitoring and symptom management. Clinical advice from the British Thoracic Oncology Group (BTOG) to NICE[13] is that BSC consists of active monitoring which normally includes computed

tomography (CT) scan approximately every 3 months and may potentially include PET scans with or without biopsies to confirm disease recurrence.

2.3.1 Durvalumab

Durvalumab is recommended by NICE (TA798)[14] as a treatment option for patients with locally advanced unresectable NSCLC whose tumours express programmed cell death-ligand 1 (PD-L1) on ≥1% of cells and whose disease has not progressed after platinum-based CRT. However, clinical advice to the company and to the EAG is that, in NHS practice, patients with unresectable locally advanced EGFRm-positive NSCLC are not routinely treated with durvalumab. The company highlighted (CS, Section 1.3.3) that:

- in the PACIFIC trial,[15] progression-free survival (PFS) and overall survival (OS) results were similar between the durvalumab (n=29) and placebo (n=14) treatment arms for patients with unresectable locally advanced EGFRm-positive NSCLC
- it is recommended in the European Society for Medical Oncology (ESMO) expert consensus statements on the management of EGFRm-positive NSCLC[16] that patients with unresectable locally advanced EGFRm-positive NSCLC should not be treated with durvalumab
- patients with EGFRm-positive NSCLC who receive durvalumab commonly experience immune-related AEs including pneumonitis.[17]

The EAG notes that real world evidence from two retrospective cohort studies, the Nassar study[18] and the Aredo study,[17] supports the view that PFS and OS results are similar for patients with EGFRm-positive NSCLC after CRT who are treated with durvalumab and for patients who receive BSC only.

Clinical advice to the EAG is that, for patients with EGFRm-positive locally advanced unresectable NSCLC after CRT, EGFR-targeted therapy would be prioritised and therefore these patients would be treated with osimertinib and not with a PD-L1 inhibitor (i.e., durvalumab).

2.4 Critique of company's definition of decision problem

A summary of the final scope[19] issued by NICE and the decision problem addressed by the company is presented in Table 1. More information regarding key issues is provided in Section 2.4.1 to Section 2.4.7.

Table 1 Summary of the decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Intervention	Osimertinib	As per NICE scope.	As per NICE scope.
Population	Adults with EGFRm-positive (exon 19 deletion or exon 21 [L858R] substitution, either alone or in combination with other EGFR mutations) locally advanced unresectable NSCLC whose disease has not progressed after platinum based chemoradiation.	As per NICE scope.	As per NICE scope.
Comparator(s)	• Durvalumab (for people who had concurrent chemoradiation therapy and have PD-L1 positive NSCLC) • Best supportive care	**Best supportive care** Best supportive care, consisting of active monitoring, represents the current SoC for patients with EGFRm-positive locally advanced unresectable NSCLC after CRT. The company excluded durvalumab as a comparator. Durvalumab is recommended by NICE (TA798)[14] as a maintenance treatment for unresectable NSCLC after CRT, but it is not recommended in current ESMO expert consensus statements.[16] Clinical advice to the company is that durvalumab is not used post-CRT for patients with EGFRm-positive NSCLC in NHS clinical practice.	Clinical advice to the EAG agrees with clinical advice to the company that patients with unresectable locally advanced EGFRm-positive NSCLC are not routinely treated with durvalumab in NHS clinical practice.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Outcomes	The outcome measures to be considered include: • OS • PFS • DFS • response rates • AEs of treatment • HRQoL	As per scope with the exception of DFS The company considers that DFS is not an appropriate outcome for this appraisal. The company stated that DFS is typically used in clinical trials of adjuvant therapies after complete tumour resection. The LAURA trial included patients with unresectable NSCLC and did not assess DFS.	Clinical advice to the EAG agrees that DFS is not an appropriate outcome for this appraisal because it is difficult to confirm that patients are disease-free after CRT and therefore PFS is a more relevant outcome.
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	[a]	As per the NICE reference case.
Subgroups	If the evidence allows, then the following subgroups will be considered: • people who had CCRT or SCRT • PD-L1 expression • disease stage • newly diagnosed or recurrent NSCLC (including post-surgery recurrence) • treatments had at previous stages (if any) • type of EGFRm	The LAURA trial included the following pre-specified subgroups (CS, Section 2.7): age (<65 years vs ≥65 years), sex, smoking status (current/former vs non-smoker), race (Asian vs non-Asian), prior CRT (CCRT vs SCRT), disease stage prior to CRT (IIIA vs IIIB/IIIC), EGFRm (Ex19del or L858R) and response to prior CRT. The company did not present subgroup analyses by: PD-L1 expression, newly diagnosed vs recurrent NSCLC and treatments at previous stages. These were not pre-specified LAURA trial subgroups. The company considered that the osimertinib treatment effect was consistent across subgroups and therefore did not present subgroup cost effectiveness results.	The company provided PFS subgroup analysis results (CS, Figure 16) for three of the six subgroups listed in the final scope[19] issued by NICE: • people who had CCRT or SCRT • disease stage • type of EGFRm

[a] The company did not present 'Economic analysis' in CS, Table 1

AE=adverse event; CCRT=concurrent chemoradiation; CRT=chemoradiation; CS=company submission; DFS=disease-free survival; EAG=External Assessment Group; EGFRm=epidermal growth factor receptor mutation; ESMO=European Society for Medical Oncology; Ex19del=exon 19 deletion; HRQoL=health-related quality of life; L858R=substitution of a leucine with an arginine at position 858 in exon 21; NHS=National Health Service: NSCLC=non-small cell lung cancer; OS=overall survival; PD-L1=programmed cell-death ligand 1; PFS=progression-free survival; PPS=post-progression survival; PPS= QALY=quality adjusted life year; SCRT=sequential chemoradiation; SoC=standard of care

Source: CS, Table 1

2.4.1 Evidence sources

Direct clinical effectiveness evidence for osimertinib is available from the LAURA trial.[20] The LAURA trial is an ongoing, phase III, multi-centre, international, double-blind, randomised, placebo-controlled trial of osimertinib versus placebo for patients with EGFRm-positive locally advanced unresectable NSCLC whose disease has not progressed during or after platinum-based CRT.

2.4.2 Population

The population addressed by the company matches the population specified in the final scope[19] issued by NICE and is in line with the anticipated UK licensed indication for osimertinib (see Section 2.2.3 and CS, Table 2).

Clinical advice to the EAG is that overall the baseline characteristics of the LAURA trial patients are representative of NHS patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT, with the exceptions that, compared with NHS patients, a higher proportion of LAURA trial patients were Asian and no LAURA trial patients were black. Clinical advice to the EAG is that the effectiveness of osimertinib is unlikely to be affected by ethnicity.

2.4.3 Intervention

The company has presented evidence for osimertinib as per the population defined in the final scope[19] issued by NICE. Further details are provided in Section 2.2.3.

2.4.4 Comparator

The company has presented direct clinical effectiveness evidence from the LAURA trial for the comparison of osimertinib versus placebo (as a proxy for BSC). Clinical advice to the EAG is that LAURA trial patients received concomitant medications (CS, Table 10) that reflect BSC in NHS clinical practice.

The company considered (and clinical advice to the EAG agrees) that durvalumab is not a relevant comparator for this appraisal. Clinical advice to the company and to the EAG is that, in NHS clinical practice, patients with EGFRm-positive locally advanced unresectable NSCLC are not routinely treated with durvalumab.

2.4.5 Outcomes

Clinical advice to the EAG is that the outcomes listed in the final scope[19] issued by NICE, with the exception of disease-free survival (DFS), are the most relevant outcomes for patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or

following CRT. The company considered (CS, Table 1), and clinical advice to the EAG agrees, that DFS was not an appropriate outcome for this appraisal as it is difficult to confirm that patients are disease free following CRT and therefore very few patients are considered disease-free at baseline. DFS was not assessed in the LAURA trial.

2.4.6 Economic analysis

As specified in the final scope[19] issued by NICE, the cost effectiveness of osimertinib was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 38.6 year time period (which the company considered was equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

Osimertinib is available to the NHS at a confidential Patient Access Scheme (PAS) price for this indication and a Commercial Access Agreement (CAA) price for the metastatic setting. Cost effectiveness results generated using discounted prices for all drugs are presented in a confidential appendix.

The EAG agrees with the company that a severity weighting is not applicable for this appraisal (CS, p151).

2.4.7 Subgroups

The company provided PFS subgroup analysis results (CS, Figure 16) for all LAURA trial pre-specified subgroups which included three of the six subgroups specified in the final scope[19] issued by NICE (i.e., subgroup analysis stratified by patients who previously received concurrent chemoradiotherapy [CCRT] versus sequential chemoradiotherapy [SCRT], disease stage and type of EGFRm).

The EAG requested (clarification question A2) subgroup analysis results for LAURA trial key secondary outcomes, namely central nervous system (CNS) PFS and OS. In response to clarification question A2, the company stated that the “LAURA trial was not powered to detect significant differences between treatment arms for other endpoints” and therefore the company did not provide LAURA trial CNS PFS and OS subgroup analysis results.

In response to clarification question A1, the company confirmed that tumour PD-L1 expression levels were not assessed at baseline in the LAURA trial and therefore it was not possible to present subgroup analysis results stratified by tumour PD-L1 expression levels.

3 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical effectiveness evidence submitted by the company to support the use of osimertinib as a maintenance therapy for patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT.

3.1 Critique of the review methods

The company conducted a systematic literature review (SLR) to identify and select clinical effectiveness evidence. Full details of the company's methods are presented in the CS (CS, Appendix D). The company's literature searches were comprehensive and were updated <6 months before the company's evidence submission to NICE. An assessment of the extent to which the company's SLR was conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 2. The EAG considers that the company's systematic review methods were appropriate.

Table 2 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D.1.2, Table 1.
Were appropriate sources searched?	Yes	See CS, Appendix D.1.1.1.
Was the timespan of the searches appropriate?	Yes	See CS, Appendix D.1.2, Table 1. No date restrictions were applied to the publication year in the company search strategies and therefore sources were searched from database inception.
Were appropriate search terms used?	Yes	See CS, Appendix D.1.1.3.
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D.1.2, Table 1.
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix D.1.2.
Was data extracted by two or more reviewers independently?	Yes	See company response to clarification question C2. One reviewer extracted data, and these data were checked by a second (independent) reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	See CS, Section 2.5 and Appendix D.3. The company assessed the quality of the LAURA trial using the NICE Quality Assessment Tool.[21]
Was the quality assessment conducted by two or more reviewers independently?	Yes	See company response to clarification question C2. One reviewer quality assessed the LAURA trial and the quality assessment was checked by a second (independent) reviewer.
Were attempts to synthesise evidence appropriate?	NA	No ITCs were required.

CS=company submission; EAG=External Assessment Group; ITC=indirect treatment comparison; NA=not applicable; NICE=National Institute for Health and Care Excellence
Source: EAG in-house checklist

3.2 Critique of the LAURA trial

3.2.1 Included trials

The company identified one trial, the LAURA trial, that provided clinical effectiveness evidence for the comparison of osimertinib versus placebo (see Section 3.2.2 to Section 3.5.5 for more trial details).

3.2.2 Characteristics of the LAURA trial

The key characteristics of the LAURA trial are presented in Table 3.

Table 3 Key characteristics of the LAURA trial

Trial parameter	LAURA trial (N=216)
Design	• Ongoing, phase III, multi-centre, international, double-blind, randomised, placebo-controlled trial • 121 centres across 17 countries in Europe, Asia-Pacific, North America and South America
Population	• Patients (≥18 years [and ≥20 years in Japan]) with histologically confirmed locally advanced, unresectable primary NSCLC predominantly non-squamous pathology • Disease positive for one of two common EGFR-sensitising mutations (Ex19del or L858R) either alone or in combination with other EGFR mutations • WHO PS 0 to 1 • Previous CCRT or SCRT including ≥2 platinum-based chemotherapy cycles and a total dose of radiation of 60Gy±10% (54Gy to 66Gy); chemoradiation must have been completed ≤6 weeks prior to randomisation • No disease progression during or following definitive platinum-based CRT
Intervention	80mg QD oral osimertinib (n=143) • dose reductions to 40mg QD oral osimertinib and dose interruptions permitted for patients who experience clinically significant AEs or unacceptable toxicity • rechallenge with 80 mg QD oral osimertinib was not permitted • patients may continue osimertinib treatment post-BICR-confirmed progression if their treating physician considers that they are still receiving clinical benefit
Comparator	Matching placebo (n=73) • placebo arm patients are permitted to switch to open-label osimertinib after BICR-confirmed progression
Primary outcome	PFS by BICR according to RECIST 1.1 • plus investigator-assessed PFS sensitivity analysis
Secondary outcomes	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
Data cut-offs presented in CS	Primary PFS analysis DCO: 5 January 2024

AEs=adverse events; BICR=blinded independent central review; CCRT=concurrent chemoradiation; CFB=change from baseline; CNS=central nervous system; CRT=chemoradiation; CS=company submission; DCO=data cut-off; 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; PFS2=second progression-free survival; PRO=patient reported outcome; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumours; SCRT=subsequent chemoradiation; 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; WHO=World Health Organisation
Source: CS, Table 5 and Table 6

3.2.3 Characteristics of patients in the LAURA trial

The baseline characteristics of the LAURA trial patients are presented in Table 4.

Clinical advice to the EAG is that, overall, the baseline characteristics of the LAURA trial patients are representative of NHS patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT. However, compared to NHS patients:

- a higher proportion of LAURA trial patients were Asian (178/216, 82.4%; CS, Table 7)
- no LAURA trial patients were black[20] .

Clinical advice to the EAG is that, for patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT, the clinical effectiveness of osimertinib is unlikely to be affected by ethnicity. Clinical advice to the EAG is that clinical practice in the included Asian countries (see Table 4) is similar to NHS clinical practice, and that patients in Asian countries have access to the same treatments as those offered to NHS patients.

In the LAURA trial, baseline characteristics were balanced across the treatment arms with the exceptions that, compared to the osimertinib arm, the placebo arm included a higher proportion of patients who:

- were aged ≥75 years (osimertinib=13/143, 9.1%; placebo=14/73, 19.2%)
- had World Health Organisation performance status (WHO PS) 1 (osimertinib=63/143, 44.1%; placebo=42/73, 57.5%)
- achieved stable disease in response to prior CRT (osimertinib=61/143, 42.7%; placebo=37/73, 50.7%) and a lower proportion of patients who achieved a partial response (osimertinib=67/143, 46.9%; placebo=27/73, 37.0%).

Clinical advice to the EAG is that the differences between the treatment arms are not concerning because:

- the median age of patients was similar (osimertinib=62 years; placebo=64 years)
- WHO PS is a subjective measure and there can be little difference in fitness between patients who have WHO PS 0 and patients who have WHO PS 1.

Table 4 Baseline characteristics of the LAURA trial patients

Baseline characteristic	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)
Race, n (%)		
Asian	116 (81.1)	62 (84.9)
White	20 (14.0)	10 (13.7)
American Indian or Alaskan Native	2 (1.4)	1 (1.4)
Black	0 (0)	0 (0)
Other	5 (3.5)	0 (0)
Smoking status, n (%)		
Never smoker	102 (71.3)	49 (67.1)
Current smoker	4 (2.8)	1 (1.4)
Former smoker	37 (25.9)	23 (31.5)
WHO PS, n (%)		
0	80 (55.9)	31 (42.5)
1	63 (44.1)	42 (57.5)
AJCC stage (8th edition) at initial diagnosis, n (%)		
Stage IIIA	52 (36.4)	24 (32.9)
Stage IIIB	67 (46.9)	38 (52.1)
Stage IIIC	24 (16.8)	11 (15.1)
Histology type, n (%)		
Adenocarcinoma	139 (97.2)	69 (94.5)
Squamous cell carcinoma	3 (2.1)	2 (2.7)
Other	1 (0.7)	2 (2.7)
Prior CRT strategy, n (%)		
CCRT	131 (91.6)	62 (84.9)
SCRT	12 (8.4)	11 (15.1)
Response to prior CRT, n (%)		
CR	4 (2.8)	3 (4.1)
PR	67 (46.9)	27 (37.0)
SD	61 (42.7)	37 (50.7)
PD	0 (0)	0 (0)
Non-evaluable	11 (7.7)	6 (8.2)
Tissue EGFRm status at screening, n (%)		
Ex19del positive	74 (51.7)	43 (58.9)
L858R positive	68 (47.6)	30 (41.1)
Missing	[redacted]	[redacted]

AJCC=American Joint Committee on Cancer; CCRT=concurrent chemoradiation; CR=complete response; CRT=chemoradiation; CS=company submission; EGFRm=epidermal growth factor receptor mutation; Ex19del=exon 19 deletion; L858R=substitution of a leucine with an arginine at position 858 in exon 21; PD=progressed disease; PR=partial response; SCRT=subsequent chemoradiation; SD=stable disease; WHO PS=World Health Organization performance status
Source: CS, Table 7 and Table 8

3.2.4 Quality assessment of the LAURA trial

The company conducted a quality assessment of the LAURA trial using the NICE Quality Assessment Tool;[21] this tool was developed based on the University of York Centre for Reviews and Dissemination guidance.[22] The company's assessments and EAG comments are presented in Table 5. The EAG's assessment is that the LAURA trial is of good methodological quality.

Table 5 Quality assessment for the LAURA trial

Quality assessment item	Company assessment	EAG assessment	EAG comment
Was randomisation carried out appropriately?	Yes	Yes	Randomisation was stratified and completed using central interactive voice/web response system (CS, Table 5).
Was the concealment of treatment allocation adequate?	Yes	Yes	Randomisation was stratified and completed using central interactive voice/web response system (CS, Table 5).
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Clinical advice to the EAG is that the LAURA trial patient baseline characteristics (CS, Table 7 and Table 8) were mostly balanced across the treatment arms.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	The LAURA trial is a double-blind trial and efficacy endpoints were BICR-assessed (CS, Table 5).
Were there any unexpected imbalances in drop-outs between groups?	No	Yes	At the primary PFS analysis DCO (5 January 2024), a smaller proportion of patients in the osimertinib arm (63/143, 44.1%) had discontinued study treatment than in the placebo arm (66/73, 90.4%; CS, Section 2.3.2).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	-

BICR=blinded independent central review; DCO=data cut-off; CS=company submission; EAG=External Assessment Group; PFS=progression-free survival
Source: CS, Table 16 and CS, Appendix D.3, Table 3

3.2.5 Statistical approach adopted for the analysis of the LAURA trial data

In response to clarification question C1, the company provided the LAURA trial Clinical Study Report (CSR) for the 5 January 2024 data cut-off (DCO),[23] the LAURA trial statistical analysis plan (TSAP) version 3.0[24] and the LAURA trial protocol version 5.0.[25] The company also summarised the statistical methods adopted for the analysis of LAURA trial data (CS, Section 2.4). A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse LAURA trial data is provided in Table 6.

Table 6 EAG assessment of statistical approaches used in the LAURA trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	See CS, Table 5 (for pre-specified subgroup analyses) and Table 12 (for population analysis sets) and LAURA trial TSAP v3.0,[24] Section 2.
Was an appropriate sample size calculation pre-specified?	Yes	See CS, Section 2.4.4.
Were all protocol amendments made prior to analysis?	Yes	A summary of the LAURA trial protocol amendments made between protocol v1.0 (23 March 2018)[26] and protocol v5.0 (3 November 2023) was provided in protocol v5.0.[25] The EAG considers that all protocol amendments were appropriate and notes that all were made prior to the first DCO date (Primary PFS analysis DCO: 5 January 2024).
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	See LAURA trial protocol v5.0,[25] Section 9.4.1.1 and Section 9.4.1.2 and LAURA trial TSAP v3.0,[24] Section 3 and Section 4.2.7 to 4.2.8.9.
Was the analysis approach for PROs appropriate and pre-specified?	Yes	See LAURA trial protocol v5.0,[25] Section 8.1.3 and LAURA trial TSAP v3.0,[24] Section 3.3 and Section 4.2.9.
Was the analysis approach for AEs appropriate and pre-specified?	Yes	See LAURA trial protocol v5.0,[25] Section 8.2 and LAURA trial TSAP v3.0,[24] Section 3.4 and Section 4.2.10.
Was a suitable approach employed for handling missing data?	Yes	See LAURA trial TSAP,[24] Section 3.1.2.1 (for missing target lesion data), Section 3.3.1 (for missing HRQoL data) and Section 3.4.1.2 (for missing safety data)
Were all subgroup and sensitivity analyses pre-specified?	Yes	See CS, Table 5 (for pre-specified subgroup analyses) and LAURA trial TSAP v3.0,[24] Section 4.2.7.2 (for PFS sensitivity analysis), Section 4.2.7.3 (for PFS subgroup analyses), Section 4.2.8.1 (for CNS PFS sensitivity analysis).

AE=adverse event; CNS=central nervous system; CS=company submission; DCO=data cut-off; EAG=External Assessment Group; HRQoL=health-related quality of life; PFS=progression-free survival; PRO=patient reported outcome; TSAP=trial statistical analysis plan
Source: CS, Table 5 and Table 12; LAURA trial protocol v5.0;[25] LAURA trial TSAP v3.0[24]

3.3 LAURA trial efficacy results

LAURA trial results from the 5 January 2024 DCO are presented in Table 7.

These data show that the LAURA trial PFS, CNS PFS, depth of response, time to death or distant metastases (TTDM), time to treatment discontinuation or death (TTD), time to first subsequent therapy (TFST), time to second subsequent therapy (TSST) hazard ratios (HRs) and the objective response rate (ORR) odds ratio (OR) statistically significantly favoured osimertinib over placebo. OS and second progression-free survival (PFS2) HRs numerically

favoured osimertinib over placebo; however, the HRs were not statistically significant, and the confidence intervals (CIs) were wide and crossed 1. The investigator-assessed PFS and CNS PFS results were consistent with the blinded independent central review (BICR)-assessed PFS and CNS PFS results.

Table 7 LAURA trial efficacy results

	Osimertinib (n=143)	Placebo (n=73)
BICR-assessed PFS		
Median (range) follow-up (months)	[redacted]	[redacted]
Number of events, n (%)	57 (39.9)	63 (86.3)
Median PFS (months) (95% CI)	39.13 (31.51 to NE)	5.55 (3.71 to 7.43)
HR (95% CI); p-value	0.16 (0.10 to 0.24); p<0.0001	
PFS rate at 6 months, % (95% CI)	[redacted]	[redacted]
PFS rate at 12 months, % (95% CI)	73.7 (65.4 to 80.3)	21.8 (13.0 to 32.1)
PFS rate at 18 months, % (95% CI)	[redacted]	[redacted]
PFS rate at 24 months, % (95% CI)	65.1 (56.4 to 72.6)	12.5 (5.9 to 21.6)
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	
BICR-assessed CNS PFS		
Median (range) follow-up (months)	[redacted]	[redacted]
Number of events, n (%)	29 (20.3)	30 (41.1)
Median PFS (months) (95% CI)	NE (NE to NE)	14.88 (7.36 to NE)
HR (95% CI); p-value	0.17 (0.09 to 0.32); p<0.001	
CNS PFS rate at 12 months, % (95% CI)	[redacted]	[redacted]
CNS PFS rate at 24 months, % (95% CI)	[redacted]	[redacted]
Investigator-assessed CNS PFS		
HR (95% CI); p-value	0.19 (0.10 to 0.36); NR	
OS		
Median (range) follow-up (months)	[redacted]	[redacted]
Number of events, n (%)	[redacted]	[redacted]
Median OS (months) (95% CI)	53.95 (46.49 to NE)	NE (42.05 to NE)
HR (95% CI); p-value	0.81 (0.42 to 1.56); p=0.530	
OS rate at 12 months, % (95% CI)	[redacted]	[redacted]
OS rate at 24 months, % (95% CI)	[redacted]	[redacted]
OS rate at 36 months, % (95% CI)	[redacted]	[redacted]
OS rate at 48 months, % (95% CI)	[redacted]	[redacted]

	Osimertinib (n=143)	Placebo (n=73)
BICR-assessed ORR		
ORR, n (%; 95% CI)	82 (57.3; 48.8 to 65.6)	24 (32.9; 22.3 to 44.9)
OR (95% CI); p-value	2.77 (1.54 to 5.08); [redacted]	
DCR, n (%; 95% CI)	127 (88.8%; 82.5 to 93.5)	58 (79.5%; 68.4 to 88.0)
OR (95% CI); p-value	2.06 (0.94 to 4.47); NR	
CR, n (%)	3 (2.1)	1 (1.4)
PR, n (%)	79 (55.2)	23 (31.5)
SD,[a] n (%)	45 (31.5)	34 (46.6)
PD, n (%)	11 (7.7)	12 (16.4)
Not evaluable, n (%)	5 (3.5)	3 (4.1)
Median DoR, months (95% CI)	36.9 (30.1 to NE)	6.5 (3.6 to 8.3)
BICR-assessed depth of response		
Median best percentage CFB in tumour size	43.3	21.9
Least square means difference, % (95% CI)	[redacted]	
BICR-assessed TTDM		
Number of events, n (%)	33 (23.1)	31 (42.5)
HR (95% CI); p-value	0.21 (0.11 to 0.38); p<0.001	
TTD		
Median TTD, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
TFST		
Number of events, n (%)	[redacted]	[redacted]
Median TTST, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	
PFS2		
Number of events, n (%)	[redacted]	[redacted]
Median PFS2, months (95% CI)	48.20 (44.42 to NE)	47.38 (28.22 to NE)
HR (95% CI); p-value	[redacted]	
TSST		
Number of events, n (%)	[redacted]	[redacted]
Median TSST, months (95% CI)	[redacted]	[redacted]
HR (95% CI); p-value	[redacted]	

[a] Disease stable for ≥8 weeks

BICR=blinded independent central review; CFB=change from baseline; CI=confidence interval; CNS=central nervous system; CR=complete response; CS=company submission; DCR=disease control rate; DoR=duration of response; HR=hazard ratio; NE=not estimable; NR=not reported; ORR=objective response rate; OR=odds ratio; OS=overall survival; PD=progressed disease; PFS=progression-free survival; PFS2=second progression-free survival; PR=partial response; SD=stable disease; TFST=time to first subsequent therapy; TSST=time to second subsequent therapy; TTD=time to treatment discontinuation or death; TTDM=time to death or distant metastases

Source: CS, Table 14 to Table 17, Table 19, Figure 6, Figure 7, Figure 15 and Section 2.6.1.2.5 to Section 2.6.1.3.3

3.3.1 EAG critique of LAURA trial efficacy results

Osimertinib treatment effect versus placebo

The LAURA trial results demonstrate a large treatment effect that strongly favours osimertinib over placebo. The EAG considers that a positive treatment effect would be expected versus placebo (i.e., no active treatment) but agrees that placebo is an appropriate proxy for BSC.

LAURA trial placebo arm PFS results may be lower than PFS for NHS patients treated with BSC

Clinical advice to the company[12] was that LAURA trial placebo arm results were "poor" compared to results expected in NHS clinical practice. Clinical advice to the EAG is that outcomes for NHS patients with EGFRm-positive locally advanced unresectable NSCLC following CRT are uncertain.

The company identified (CS, Section 3.3.4) six studies[18,27-31] that reported PFS for patients with EGFRm-positive locally advanced unresectable NSCLC following CRT. Key PFS results from the identified studies are presented in Table 8; the EAG has not presented PFS results from the Neal study[27] because most Neal study[27] patients received EGFR-TKIs following CRT and therefore the results are not a suitable proxy for PFS results for patients receiving placebo or BSC.

LAURA trial placebo arm median PFS was lower than median PFS reported in the five identified studies[18,28-31] for patients who were treated with placebo or BSC (Table 8). Two of the identified studies (the PACIFIC trial[30] and the SOLUTION study[31]) used the same PFS definition as the LAURA trial and calculated PFS from **completion** of CRT. Three of the identified studies[18,28,29] calculated PFS from **initiation** of CRT and therefore median PFS and PFS rates reported in these studies[18,28,29] were higher than if the LAURA trial PFS definition was used. The EAG notes that PACIFIC trial[30] PFS was BICR-assessed whereas the other four studies[18,28,29,31] were retrospective observational studies that reviewed patient records and PFS in these studies was investigator-assessed.

Table 8 PFS reported for patients with EGFRm-positive locally advanced unresectable NSCLC following CRT

Study	Population	Intervention	Median PFS, months (95% CI)	PFS rates, % (95% CI)
LAURA trial (BICR-assessed)	Patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed following CRT (n=73)	Placebo	5.55 (3.71 to 7.43)	2-year: 2.5 (5.9 to 21.6) 3-year: [redacted]
LAURA trial (investigator-assessed)			7.3 (5.5 to 10.3)	2- and 3-year: [redacted]
PACIFIC trial[30]	Patients with EGFRm-positive Stage III unresectable NSCLC that has not progressed following CRT (n=11)	Placebo	10.9 (1.9 to NE)	NR
SOLUTION study[31]	Patients with EGFRm-positive Stage III unresectable NSCLC that has not progressed following CRT (n=29)	BSC (prior to the approval of durvalumab and ICIs)	16.9 (NR)	3 to 4 years: ~20%
Tanaka study[28]	Patients with EGFRm-positive Stage III adenocarcinoma that has not progressed following CRT (n=29)	Active monitoring	9.8 (7.6 to 19.0)[a]	2-year: 7.7%
Nassar study[18]	Patients with EGFRm-positive Stage III unresectable NSCLC that has not progressed following CRT (n=47)	Active monitoring	9.7 (6.1 to 12.0)[a]	2-year: 27%
Akamatsu study[29]	Patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed following CRT (n=13)	Active monitoring	9.6 (NR)[a]	NR

[a] PFS calculated from initiation of CRT
BICR=blinded independent central review; BSC=best supportive care; CI=confidence interval; CRT=chemoradiation; CS=company submission; CSR=clinical study report; EGFRm=epidermal growth factor receptor mutation; ICI=immune checkpoint inhibitor; NE=not estimable; NR=not reported; NSCLC=non-small cell lung cancer; PFS=progression-free survival
Source: CS, Table 14, Table 37 and Figure 6; CSR appendices,[23] Table 14.2.1.1.1; Naidoo 2023;[30] Horinouchi 2020;[31] Tanaka 2015;[29] Nassar 2024;[18] Akamatsu 2014[29]

The osimertinib OS treatment effect is not statistically significant versus placebo

The EAG notes that while median PFS was statistically significantly improved with osimertinib versus placebo, the PFS gain has not translated into an OS gain. The company attributed (CS, p66) this to crossover; 50/73 (68.5%) LAURA trial placebo arm patients received osimertinib after first progression. In the LAURA trial, placebo patients were permitted to switch to open-label osimertinib after BICR-confirmed progression. Clinical advice to the EAG is that this is reflective of current NHS clinical practice as most NHS patients with EGFRm-positive locally advanced unresectable NSCLC that has progressed after CRT are treated with osimertinib.

The EAG however notes that 42/143 (29.4%) LAURA trial osimertinib arm patients received a subsequent anticancer treatment after discontinuing osimertinib (Table 9) including 28/63 (44.4%) osimertinib arm patients who received a subsequent EGFR-TKI and 15/63 (23.8%) osimertinib arm patients who were rechallenged with osimertinib. Clinical advice to the EAG is that rechallenge with osimertinib or another EGFR-TKI would not be permitted in NHS clinical practice.

The EAG acknowledges that LAURA trial OS data were only 19.9% mature at the 5 January 2024 DCO and therefore it is difficult to draw conclusions about the osimertinib OS treatment effect.

Table 9 LAURA trial subsequent anticancer treatments

Subsequent anticancer treatment, n (%)[a]	Osimertinib (n=143)	Placebo (n=73)
Number of patients who discontinued study treatment	63 (44.1)	66 (90.4)
Number of patients who received any subsequent anticancer treatment	42 (29.4)	57 (78.1)
Subsequent anticancer treatment received[b]		
EGFR-TKI	28 (19.6) [44.4]	57 (78.1) [86.4]
First- or second-generation EGFR-TKI	12 (8.4) [19.0]	7 (9.6) [10.6]
Third-generation EGFR-TKI	16 (11.2) [25.4]	52 (71.2) [78.8]
Osimertinib	15 (10.5) [23.8]	51 (69.9) [77.3]
Aumolertinib	1 (0.7) [1.6]	1 (1.4) [1.5]
Furmonertinib	0 (0) [0]	1 (1.4) [1.5]
VEGF inhibitor	8 (5.6) [12.7]	5 (6.8) [7.6]
Cytotoxic chemotherapy	21 (14.7) [33.3]	11 (15.1) [16.7]
Platinum-based chemotherapy	19 (13.3) [30.2]	7 (9.6) [10.6]
Folic acid analogues (pemetrexed)	[redacted]	[redacted]
Taxanes	[redacted]	[redacted]
Other chemotherapy	[redacted]	[redacted]
PD-1/PD-L1 inhibitor	5 (3.5) [7.9]	1 (1.4) [1.5]
Other[c]	2 (1.4) [3.2]	2 (2.7) [3.0]
Radiotherapy	21 (14.7) [33.3]	5 (6.8) [7.6]

[a] Patients may be counted in multiple rows if they received ≥1 subsequent anticancer treatment
[b] Percentages presented in the curved brackets are calculated as the proportion of the total number of patients in each treatment arm; the percentages presented in the square brackets who are calculated as the proportion of patients who discontinued study treatment
[c] Including investigational anticancer treatments (n=2) and unknown anticancer treatments (n=2)
CS=company submission; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; PD-1=programmed cell-death protein 1; PD-L1=programmed cell-death ligand 1; VEGF=vascular endothelial growth factor
Source: CS, Table 11

3.3.2 Subgroup analyses

The company provided PFS subgroup analysis results from the 5 January 2024 DCO for all pre-specified subgroups (CS, Figure 16) which included three subgroups specified in the final scope[19] issued by NICE (i.e., subgroup analysis stratified by patients who previously received CCRT versus SCRT, disease stage and type of EGFRm). The PFS subgroup analysis HRs were generally consistent; most PFS HRs were <0.4 and represented a clinically meaningful reduction in the risk of disease progression/death for patients treated with osimertinib compared to those treated with placebo.

The non-Asian subgroup PFS HR was 0.48 (95% CI: 0.20 to 1.19); however, the non-Asian subgroup only included a very small number of patients and the number of events was low (non-Asian osimertinib patients: n=14/27; non-Asian placebo patients: n=8/11) and therefore it is difficult to draw conclusions about the PFS treatment effect for patients in this subgroup. Clinical advice to the EAG is that the effectiveness of osimertinib is unlikely to be affected by

ethnicity for patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT.

3.4 Patient reported outcomes from the LAURA trial

In the LAURA trial, health-related quality of life (HRQoL) data were collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire lung cancer module (EORTC QLQ-LC13), EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) and EuroQol visual analogue scale (VAS).

In response to clarification question A4, the company provided EORTC QLQ-C30 and EORTC QLQ-LC13 results. Baseline EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L subscale and item scores and EuroQol VAS scores were similar between treatment arms (CSR appendices,[23] Table 14.2.10.2.3, Table 14.2.10.2.4, Table 14.2.11.3 and Table 14.2.11.4, respectively).

3.4.1 Change from baseline for EORTC QLQ-C30 and EORTC QLQ-LC13 scores

The company presented (CS, Table 20) change from baseline (CFB) for EORTC QLQ-C30 and EORTC QLQ-LC13 subscale and item scores analysed using a mixed-effect model for repeated measures (MMRM).

The CFB EORTC QLQ-C30 and EORTC QLQ-LC13 MMRM results showed no clinically meaningful improvement (i.e., ≥10 point increase) or clinically meaningful worsening (i.e., ≥10 point decrease) of EORTC QLQ C-30 or EORTC QLQ LC-13 scores from baseline in either treatment arm.

3.4.2 Time to clinically meaningful deterioration in EORTC QLQ-C30 and EORTC QLQ-LC13 scores

A slightly higher proportion of patients in the osimertinib arm ([redacted]/131, [redacted]) experienced a clinically meaningful worsening in EORTC QLQ-C30 global health status (GHS) score or death than in the placebo arm ([redacted]/68, [redacted]). The time to deterioration HRs for the reported EORTC QLQ-C30 and EORTC QLQ-LC13 subscale and item scores (CS, Table 21) showed that time to deterioration was longer in placebo arm than in the osimertinib arm, with exception of appetite loss, however, the CIs were wide and crossed 1.

3.4.3 EuroQol VAS score

Mean baseline EuroQoL VAS scores were >76 in both treatment arms (CS, Section 2.6.1.4.5) and remained similar to baseline over time ([redacted]; CSR appendices, Table 14.2.11.4).

3.5 Safety and tolerability results from the LAURA trial

LAURA trial safety results from the 5 January 2024 DCO are summarised in Section 3.5.1 to Section 3.5.5. Median total duration of treatment was longer in the osimertinib arm (23.98 months, range: [redacted] to [redacted] months) than in the placebo arm (8.31 months, range: [redacted] to [redacted] months; CS, Table 22). At the time of the 5 January 2024 DCO (CS, Section 2.3.3), a higher proportion of patients in the osimertinib arm (80/143, 55.9%) were still receiving their randomised treatment than in the placebo arm (7/73, 9.6%; CS, Section 2.3.2).

3.5.1 Adverse events

Nearly all osimertinib arm patients (140/143, 97.9%) and most placebo arm patients (64/73, 87.7%) experienced ≥1 adverse event AE of any grade (CS, Table 23).

The most common any grade AEs (CS, Table 24) were radiation pneumonitis (osimertinib: 68/143, 48%; placebo: 28/73, 38%), diarrhoea (osimertinib: 51/143, 36%; placebo: 10/73, 14%), rash (osimertinib: 34/143, 24%; placebo: 10/73, 14%) and COVID-19 (osimertinib: 29/143, 20%; placebo: 6/73, 8%).

A higher proportion of patients in the osimertinib arm (50/143, 35.0%) experienced ≥1 Grade ≥3 AEs than in the placebo arm (9/73, 12.3%; CS, Table 23). The most common Grade ≥3 AEs (CS, Table 26) in the osimertinib arm were pneumonia (4/143, 2.8%), radiation pneumonitis (3/143, 2.1%) and diarrhoea (3/143, 2.1%). The most common Grade ≥3 AE in the placebo arm was pneumonia (3/73, 4.1%).

3.5.2 Treatment discontinuations

Overall, a lower proportion of patients in the osimertinib arm (63/143, 44.1%) discontinued study treatment than in the placebo arm (66/73, 90.4%; CS, Section 2.3.2). However, a higher proportion of patients in the osimertinib arm discontinued treatment due to AEs (18/143, 12.6%) due to AEs than in the placebo arm (4/73, 5.5%; CS, Table 23). The most common reason for treatment discontinuation in both treatment arms was BICR-assessed disease progression (osimertinib: 36/143, 25.2%; placebo: 54/73, 74.0%; CS, Section 2.3.2).

3.5.3 Dose modifications

A higher proportion of patients in the osimertinib arm required dose reductions and/or interruptions (80/143, 55.9%) due to AEs than in the placebo arm (18/73, 24.7%; CS, Table 23).

3.5.4 Adverse events of special interest

Clinical advice to the EAG is that pneumonitis is an adverse event of special interest (AESI); however, pneumonitis is rare and is well managed in NHS clinical practice by treatment with high-dose steroids and either dose interruptions or treatment discontinuation. A higher proportion of patients in the osimertinib arm (8/143, 5.6%) experienced pneumonitis than in the placebo arm (1/73, 1.4%; CS, Table 24).

3.5.5 Deaths

Deaths due to AEs were very uncommon in both treatment arms ([redacted]; CS, Table 23).

3.6 Summary and clinical effectiveness conclusions

The company provided clinical effectiveness evidence for the comparison of osimertinib versus placebo (as a proxy for BSC) from the LAURA trial, an ongoing phase III randomised, placebo-controlled trial. The EAG considers that the LAURA trial is a well-conducted trial of good methodological quality.

Clinical advice to the EAG is that the LAURA trial results are generalisable to NHS patients because the baseline characteristics of the LAURA trial patients are mostly representative of NHS patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT, with the exceptions that, compared with NHS patients, a higher proportion of LAURA trial patients were Asian and no LAURA trial patients were black. Clinical advice to the EAG is that the effectiveness of osimertinib is unlikely to be affected by ethnicity.

The LAURA trial results showed that compared with placebo, maintenance treatment with osimertinib statistically significantly improved PFS, CNS PFS, depth of response, TTDM, TTD, TFST, TSST and ORR. Overall, the LAURA trial HRQoL results showed no clinically meaningful improvement or worsening from baseline in either treatment arm; over time, scores remained similar to baseline scores.

Clinical advice to the company[12] was that the LAURA trial placebo arm results were “poor” compared to results expected in NHS clinical practice. Clinical advice to the EAG is that outcomes for NHS patients with EGFRm-positive locally advanced unresectable NSCLC following CRT are uncertain.

Compared with placebo, maintenance treatment with osimertinib numerically improved OS and PFS2. At the time of the 5 January 2024 DCO, the LAURA trial OS data were 19.9% mature and 50/73 (80.6%) placebo arm patients had received osimertinib after first

progression. It is therefore difficult to draw conclusions about the osimertinib OS treatment effect.

3.6.1 Safety conclusions

Clinical advice to the EAG is that osimertinib is tolerable and that the AEs associated with osimertinib are manageable in NHS clinical practice.

4 COST EFFECTIVENESS EVIDENCE

This section provides a summary of the economic evidence submitted by the company in support of osimertinib for maintenance treatment of EGFRm-positive locally advanced unresectable NSCLC whose disease has not progressed during or following platinum-based CRT. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft® Excel.

4.1 Company review of published cost effectiveness evidence

The company undertook a SLR to identify and appraise i) published cost effectiveness evaluations, ii) HRQoL data, and iii) healthcare resource use (HCRU) and cost data relevant to the decision problem. The SLR target population was broadly defined as adults with locally advanced unresectable Stage III NSCLC or populations with mixed stages of NSCLC with at least 80% of the population having Stage III disease. Economic evaluations were restricted to those focusing on any pharmacological intervention administered in maintenance settings after CRT in unresectable locally advanced Stage III NSCLC.

Electronic database searches were originally conducted on 18th May 2023, with the most recent update conducted on 20th August 2024. No language restriction was specified and only English language studies were included in the review. Economic evaluations and costing studies were included if published between 2013 and 2023 and searches for studies reporting HRQoL data were restricted to those published from 2002 onwards. The company also conducted searches of the grey literature, these included manual searches of:

- conference proceedings, to identify abstracts published between January 2020 and September 2024
- Health Technology Assessment (HTA) agency websites, to identify relevant studies published since 2013
- clinical trial registries, to identify all relevant observational studies relating to the intervention and comparators of interest

The bibliographies of all relevant SLRs, HTA reports and economic evaluations were hand-searched to identify any additional relevant studies. Full details of the methods used by the company to identify and select relevant cost effectiveness evidence are presented in the CS (Appendix G, Appendix H, Appendix I).

The company SLR included 14 unique economic evaluations and five HTA submissions (CS Appendix G Table 6). Three studies[14,32,33] were conducted in the UK and assessed durvalumab as a maintenance treatment for patients with locally advanced unresectable

NSCLC; none of the included economic evaluations assessed the cost effectiveness of treatments specifically for patients with locally advanced unresectable EGFRm-positive NSCLC whose disease had not progressed during or following platinum-based CRT. An additional search of NICE HTA submissions identified a further six submissions for other NSCLC indications.[34-39] Seven HRQoL studies[14,32,40-44] and 20 unique observational and costing studies were identified (CS, Appendix G, Table 6).

4.2 EAG critique of company literature review

An assessment of the extent to which the company's systematic reviews were conducted in accordance with the EAG's in-house systematic review checklist is summarised in Table 10. The EAG considers the methods used to conduct the company's systematic reviews of cost effectiveness evidence, HRQoL and healthcare resource use studies were of a good standard.

Table 10 EAG appraisal of systematic review methods

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes.
Were appropriate sources searched?	Yes.
Was the timespan of the searches appropriate?	Yes.
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	It was not clear why studies published in 2024 were excluded.
Was study selection applied by two or more reviewers independently?	Yes.
Was data extracted by two or more reviewers independently?	Data was extracted by a single reviewer and independently verified by a senior reviewer.
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes.
Was the quality assessment conducted by two or more reviewers independently?	Studies were assessed by a single reviewer and independently verified by a senior reviewer.
Were attempts to synthesise evidence appropriate?	NA.

EAG=External Assessment Group; NA=not applicable
Source: EAG in-house checklist

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

The EAG appraisal of the company's economic analyses using the NICE Reference Case checklist and Drummond checklist is presented in Table 11 and Table 12.

Table 11 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE.	Yes.
Comparators	As listed in the scope developed by NICE.	The company considered (and EAG agreed) that consolidation durvalumab was not a relevant comparator.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Yes.
Perspective on costs	NHS and PSS.	Yes.
Type of economic evaluation	Cost utility analysis with fully incremental analysis.	Yes.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Yes.
Synthesis of evidence on health effects	Based on systematic review.	Yes.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	Yes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	Yes.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Yes.

EAG=External Assessment Group; EQ-5D=EuroQol-5 Dimensions; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; PSS=Personal Social Services; QALY=quality adjusted life
Source: EAG assessment of NICE Reference Case[21]

Table 12 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	There is no statistically significant difference in OS for patients treated with osimertinib versus BSC in the latest DCO of the LAURA trial.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partial	HSUVs exceed or are close to age- and sex-matched general population utility values.
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Partial	For patients in the active monitoring arm, life years gained in the PD health state (the health state in which most patients receive osimertinib) were not compared to life years gained for patients who receive osimertinib in the metastatic setting (TA654[39]).

BSC=best supportive care; DCO=data cut-off; EAG=External Assessment Group; HSUVs=health state utility values; PD=progressed disease; OS=overall survival
Source: Drummond and Jefferson (1996)[45] and EAG comment

4.2.2 Model structure

The company developed a de novo semi-Markov cohort model in Microsoft® Excel to evaluate the cost effectiveness of osimertinib for maintenance treatment of EGFRm-positive locally advanced unresectable NSCLC whose disease had not progressed during or following platinum-based CRT. The model consists of three mutually exclusive health states (Figure 1). Patients enter the model in the progression-free (PF) health state and receive either osimertinib or BSC (active monitoring). After each model cycle, patients can remain progression-free or transition to the progressed disease (PD) health state or the dead health state. Following progression, patients can remain in the PD health state or transition to the dead health state (an absorbing health state). Transition probabilities were derived from LAURA trial data and vary over time and by treatment.

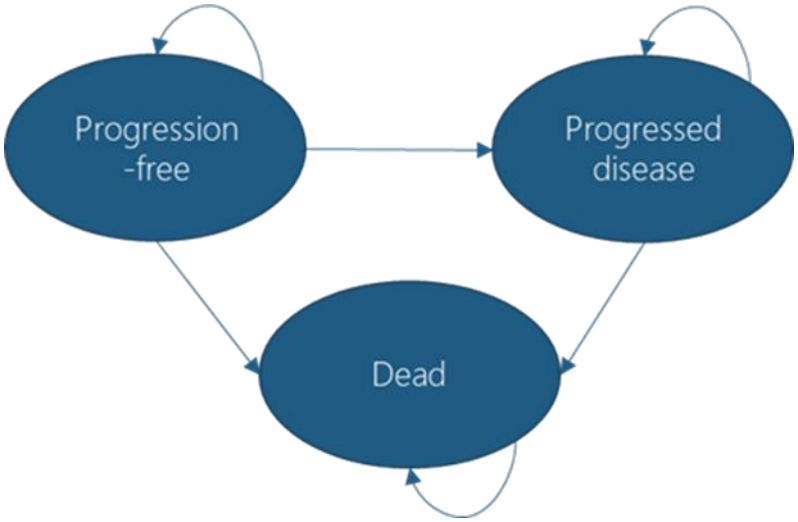

Figure 1 Company model structure

Source: CS, Figure 17

4.2.3 Population

The target population aligns with the LAURA trial intention-to treat (ITT) population, namely patients aged ≥18 years with locally advanced unresectable EGFRm-positive NSCLC whose disease has not progressed during or after platinum-based CRT. The baseline parameters used in the company model reflect LAURA trial patient baseline characteristics (Table 13). Patient body surface area (BSA) and weight were used in the model to estimate the required doses of some subsequent treatments in the metastatic setting.

Table 13 LAURA trial baseline patient characteristics used in company model

Parameter	Value (mean)
Age, years	61.4
Female, %	61
Weight, kg	62.3
Height, cm	160.80
BSA, m^2	1.67[a]

[a] Calculated using Mosteller formula (average patient height and weight)
BSA=body surface area; CS=company submission
Source: CS, Table 51 and Table 63

4.2.4 Interventions and comparators

The economic model compares the cost effectiveness of osimertinib versus BSC (active monitoring); LAURA trial placebo arm data are used as a proxy for BSC. Osimertinib is administered orally at a dose of 80mg once daily until progression or unacceptable toxicity. For patients who are progression-free, BSC consists of monitoring and healthcare resource use only (Section 4.2.8); drug costs are applied for subsequent treatments in the PD state.

4.2.5 Perspective, time horizon and discounting

The model perspective was reported as NHS and Personal Social Services (PSS). The model cycle length was 30 days and a half-cycle correction was applied to health outcomes and costs, excluding one-off costs (e.g., subsequent treatment, AE-related costs and end-of-life costs). The model time horizon, which was based on the mean age of patients at the start of the LAURA trial (61.4 years), was 38.6 years, and costs and outcomes were discounted at a rate of 3.5% per annum.

4.2.6 Treatment effectiveness and extrapolation

Transitions from the PFS health state to the PD health state (TTP)

LAURA trial time to progression (TTP) data (5 January 2024 DCO) were used to estimate the probability of progression in each model cycle for both treatment arms. TTP is defined as time from randomisation until BICR-confirmed disease progression (pre-progression deaths were censored observations).

The company assessed the proportional hazard (PH) assumption by visual inspection of log-cumulative hazard plots and results of Schoenfeld residual tests. The company concluded that the effect of treatment with osimertinib may vary over time and therefore fitted independent parametric models to LAURA trial TTP osimertinib and placebo Kaplan-Meier (K-M) data. The company fitted seven standard parametric models (exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, generalised gamma) to LAURA trial osimertinib and placebo TTP K-M data. The company considered that it was not appropriate to fit more flexible models as these may have overfitted the data and could be unduly influenced by low numbers of patients at risk towards the end of follow-up.

The company considered that the statistical fit of all distributions were similar (maximum difference in scores between distributions: Akaike information criterion [AIC]=8 points; Bayesian information criterion [BIC]=6 points) and reflected the flat hazard of progression for patients treated with osimertinib. All fitted distributions, except for the gamma and Gompertz distributions, generated median and 3-year TTP estimates that were similar to LAURA trial results. The company selected the Weibull distribution to generate TTP estimates for patients treated with osimertinib arm as this distribution had a reasonable statistical and visual fit to observed LAURA trial K-M data and four of the five clinical experts consulted during the company advisory board forum[12] considered that the Weibull distribution generated the most clinically plausible extrapolation of LAURA trial TTP data for patients treated with osimertinib.

For patients treated with BSC, the company considered that the generalised gamma, lognormal and loglogistic distributions had the best statistical fit and provided the best visual

fit to LAURA trial TTP hazards. All distributions, except for the gamma and Gompertz distributions, underestimated LAURA trial hazards at the tail end of the K-M curve. Three of the five clinical experts consulted by the company[12] preferred the generalised gamma distribution and therefore this distribution was selected by the company to generate TTP estimates for patients receiving BSC.

The probability of progression in each model cycle for each treatment was calculated using the hazards from the selected TTP curve.

Transitions from PFS to dead health state (PFS)

The probability of transitioning from the progression-free to the dead health state was calculated as the difference between the probability of remaining progression-free and alive and the probability of progression in each model cycle (derived from the selected PFS and TTP curves for each treatment). LAURA trial PFS data (5 January 2024 DCO) was used in the model; the endpoint is defined as the time from randomisation until the date of objective BICR-confirmed disease progression or death.

The company selected the same distributions to generate TTP and PFS estimates (osimertinib: Weibull; BSC: generalised gamma) as i) TTP is derived from PFS and ii) to minimise the risk of illogical crossing of TTP and PFS curves. All clinical experts consulted by the company[12] agreed that the TTP and PFS distributions selected for each treatment should be aligned. The company also considered that using the same parametric distributions to generate TTP and PFS estimates was supported by the statistical and visual fit of the Weibull and generalised gamma distributions to the LAURA trial PFS K-M osimertinib and placebo arm data, respectively.

The probability of remaining progression-free in each model cycle was calculated as the complement of the transition probabilities out of the progression-free health state:

$$TP_{PF \rightarrow PF} = 1 - TP_{PF \rightarrow PD} - TP_{PF \rightarrow D}$$

Transitions from PD to dead health state (PPS)

LAURA trial post-progression survival (PPS) data (5 January 2024 DCO) were used to estimate the probability of progression in each model cycle for patients treated with osimertinib and patients receiving placebo. PPS is defined as time from BICR-confirmed disease progression until date of death or censoring.

The company distribution selection process was the same as that previously described for TTP. The company considered that visual inspection of the Schoenfeld residuals plot provided

some evidence of non-proportional hazards and that the residuals test result lacked validity. Independent parametric models were therefore fit to LAURA trial PPS K-M data for each arm.

The company considered that the exponential and Gompertz distributions had the best statistical fit to LAURA trial osimertinib arm data. The company considered that only the generalised gamma and Gompertz distributions reflected the increase in LAURA trial post-progression death hazards. Three of the five clinicians consulted by the company[12] considered that, from the perspective of UK clinical practice, the Gompertz distribution generated the most plausible estimates. The company selected the Gompertz distribution to generate PPS estimates for patients treated with osimertinib.

The company considered that the exponential and Gompertz distributions had the best statistical fit to LAURA trial placebo arm data; however, compared with the LAURA trial, all distributions over-estimated PPS. The company considered that only the generalised gamma and Gompertz distributions reflected the increase in LAURA trial post-progression death hazards. Three of the five clinicians consulted by the company[12] considered that, from the perspective of UK clinical practice, the Gompertz distribution generated the most plausible estimates. The company selected the Gompertz distribution to generate PPS estimates for patients receiving BSC.

The probability of remaining in the PD health state in each model cycle was calculated as one minus the probability of transitioning from the PD health state to the dead health state. The probabilities of transitioning to the dead health state (from the PF and PD health states) were constrained by age- and sex-matched general population mortality. General population mortality data from 2021 were sourced from life tables published by the Office for National Statistics.[46]

4.2.7 Health-related quality of life

Health state utility values

EQ-5D-5L data (5 January 2024 DCO) were collected from LAURA trial patients at randomisation, during treatment, at progression and at survival follow-up visits. A mixed model for repeated measures was used to estimate health state utility values (HSUVs) for the PF and PD health states. EQ-5D-5L HSUVs were mapped to EQ-5D-3L values (UK value set) using the algorithm developed by the Decision Support Unit (DSU).[47] The company considered that the LAURA trial PD HSUV did not fully reflect the decline in HRQoL that occurs as disease progresses and that the PD HSUV was associated with uncertainty due to the small sample size (n=102). The company considered the PF HSUV that informed TA654[39] (derived from FLAURA trial[48] data for patients with untreated EGFRm-positive advanced NSCLC) was a

more robust estimate of HRQoL for patients in the PD health state given the larger sample (n=486). The HSUVs used in the company base case are presented in Table 14. HSUVs were adjusted to account for the decrease in HRQoL that occurs with age using general population utility values estimated by Hernandez-Alava[49] and the baseline age and sex of patients in the LAURA trial (Table 13).

Table 14 Health state utility values used in company base case

Health state	Mean (SD)	Source
PFS	[redacted]	LAURA trial
PD	0.794 (0.01)	TA654[39]

PFS=progression-free survival; PD=progressed disease; SD=standard deviation
Source: Company clarification model

Adverse event utility decrements

The company model includes all treatment-related Grade ≥3 AEs that occurred in either LAURA trial arm. The disutility and duration of each included AE were sourced from the literature (CS, Table 42). The AE-related QALY loss was calculated for each treatment arm by multiplying the LAURA trial AE incidence rate by the corresponding disutility and mean duration (in days). In the company base case, an AE-related QALY loss was applied as a one-off decrement in the first model cycle.

4.2.8 Resources and costs

Drug acquisition and administration costs

Drug acquisition costs for osimertinib are presented in Table 15. Osimertinib is available to the NHS at a confidential discounted PAS price. The LAURA trial permitted a dose reduction of osimertinib (80mg to 40mg once daily) to manage drug-related toxicities. The company did not apply the relative dose intensity multiplier from the LAURA trial as the pack size and cost are equivalent for the two strengths of osimertinib and therefore dose reductions do not affect the drug acquisition cost. The company included an administration cost (£10) for osimertinib equivalent to 12 minutes of pharmacist dispensing time.[2]

Table 15 Osimertinib dosing schedule and drug acquisition cost

Schedule	Duration	Strength	Pack size	Formulation	Pack price
80mg orally once daily	Until progression or unacceptable toxicity	80mg	30	Tablet	[redacted] (list price: £5,770)
		40mg	30	Tablet	[redacted] (list price: £5,770)

CS=company submission
Source: CS, Table 45 and Table 46

Time to treatment discontinuation

The company modelled time to TTD for patients treated with osimertinib using 36 months of LAURA trial TTD K-M data; after that an exponential distribution was assumed for the remaining model time horizon. The company justified this piecewise approach as a low number of patients remained at risk beyond 36 months. In response to clarification question B2, the company considered that the exponential distribution was the most clinically plausible distribution.

Clinical advice to the company[12] was that patients may discontinue treatment with osimertinib if, after 3 to 5 years, they remain progression-free; clinical experts also consider that it was unlikely that patients would remain on treatment indefinitely. In the base case, the company applied a 10-year TTD cap; the effect of the cap is that no patients remain on treatment with osimertinib after 10 years.

Subsequent treatment costs

In the company model, patients can receive up to two lines of subsequent treatments on progression. The distribution of subsequent treatments was informed by five clinical experts consulted by the company[12] and varied by treatment arm (Table 16).

Table 16 Subsequent treatment distributions applied in company model

Subsequent treatment	Osimertinib	BSC
% receiving ≥1 line of subsequent treatment	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]
% receiving ≥2 lines of subsequent treatment	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]

BSC=best supportive care; CS=company submission
Source: CS, Table 48 (average clinical expert estimates)[12]

Subsequent treatment durations were sourced from the literature and validated by clinical experts (CS, Table 49). To inform the treatment duration of osimertinib for patients initially treated with BSC, the company used the [redacted].[50] Clinical experts[12] considered that patients in the placebo arm of the LAURA trial who receive osimertinib post-progression would have a longer mean treatment duration than patients who received osimertinib as a first-line treatment in the metastatic setting. The company therefore increased the modelled mean osimertinib treatment duration from [redacted].

The unit costs and dosing schedules of the subsequent treatments included in the company model are presented in Table 17. LAURA trial patient characteristics (Table 13) were used to calculate subsequent treatment costs when dosing depended on patient weight or BSA. Administration costs for subsequent treatments were also included (CS, Table 53). Subsequent treatment costs were applied as a one-off cost when patients entered the PD health state.

Table 17 Subsequent treatment dosing schedules and drug acquisition costs

Drug	Schedule	Strength	Pack size	Formulation	Pack price	Source
Docetaxel	Q3W 75mg/m2 IV	20mg	1	Vial	£19.70	eMIT[51]
Paclitaxel	Q3W 175mg/m2 IV	100mg	1	Vial	£12.89	
Pemetrexed	Q3W 500 mg/m2 IV	100mg	1	Vial	£114.44	
Carboplatin	Q3W 575 mg IV	600mg	1	Vial	£38.93	
Osimertinib	QD 80 mg oral	80mg	30	Tablet	[redacted]	CAA
Radiotherapy	Once	-	1	-	£400.89	NHS Cost Collection 2023/2024,[52] HRG code: SC24Z
Atezolizumab	Q3W 1200mg IV	1,200mg	1	Vial	£3,807.69	BNF[53]
Bevacizumab	Q3W 8mg/kg IV	100mg	1	Vial	£205.00	BNF[53]
Afatinib	QD 40mg oral	40mg	28	Tablet	£2,023.28	BNF[53]
Gefitinib	QD 250mg oral	250mg	30	Tablet	£60.68	eMIT[51]

[redacted]

BNF=British National Formulary; CAA=Commercial Access Agreement; CS=company submission; eMIT=electronic Market Information Tool; HRG= Healthcare Resource Group; IV=intravenous; NHS=National Health Service; NSCLC=non-small cell lung cancer; QD=once daily; Q3W=every 3 weeks
Source: CS, Table 52 and company response to clarification question B6, Table 3 and clarification question C3

Health state and resource use costs

Healthcare resource use estimates for patients in the PF and PD health states were sourced from TA798[14] and TA654[39] respectively. The values were subsequently adjusted in line with the views of five clinical experts[12] and assigned unit costs (Table 18).

Table 18 Health state resource use estimates and unit costs

Health state	Resource use	Frequency[a]		Unit cost	Source
		Osimertinib	BSC		
PFS	Outpatient oncologist visit	1st year: [redacted] 2nd year: [redacted] Years 3 to 5: [redacted]	1st year: [redacted] 2nd year: [redacted] Years 3 to 5: [redacted]	£193	NHS National Cost Collection 2023/2024,[52] WF01A, code 370
	MRI (head)	[redacted]	[redacted]	£224	NHS National Cost Collection 2023/2024,[52] code RD05Z
	CT scan (chest)	1st year: [redacted] 2nd year: [redacted] Years 3 to 5: [redacted]	1st year: [redacted] 2nd year: [redacted] Years 3 to 5: [redacted]	£121	NHS National Cost Collection 2023/2024,[52] code RD26Z
	ECG (one off)	[redacted]	[redacted]	£90	NHS National Cost Collection 2023/2024,[52] code EY50Z
PD	Outpatient oncologist visit	[redacted]	[redacted]	£193	NHS National Cost Collection 2023/2024,[52] WF01A, code 370
	Chest radiography	[redacted]	[redacted]	£44.13	NHS National Cost Collection 2023/2024,[52] code DAPF, inflated to 2024 prices
	CT scan (chest)	[redacted]	[redacted]	£121	NHS National Cost Collection 2023/2024,[52] code RD26Z
	CT scan (Other)	[redacted]	[redacted]		
	ECG	[redacted]	[redacted]	£90	NHS National Cost Collection 2023/2024,[52] code EY50Z
	Community nurse visit	[redacted]	[redacted]	£87.76	Band 8A (1-hour patient-related work) PSSRU 2023,[54] inflated to 2024 prices
	Clinical nurse specialist	[redacted]	[redacted]	£87.76	Band 8A (1-hour patient-related work) PSSRU 2023,[54] inflated to 2024 prices
	GP surgery visit	[redacted]	[redacted]	£44.95	10 minute visit; PSSRU 2023,[54] inflated to 2024 prices
	MRI (head)	[redacted]	[redacted]	£224	NHS National Cost Collection 2023/2024,[52] code RD05Z

[a]TA798[14] and TA654[39] values adjusted in line with advice provided by clinical experts[12]
BSC=best supportive care; CS=company submission; CT=computed tomography; ECG=electrocardiogram; GP=general practitioner; MRI=magnetic resonance imaging; NHS=National Health Service; PD=progressed disease; PFS=progression-free survival; PSSRU=Personal Social Services Research Unit
Source: CS, Table 55 and Table 56

Costs associated with monitoring and treatment of CNS metastases were included as part of total PD health state costs. In the model, the proportions of patients who experienced CNS

metastases reflected the proportions of osimertinib arm and placebo arm LAURA trial patients with CNS metastases (12.6% and 35.6%, respectively). The costs included in the company model were sourced from TA536[55] (Table 19); the total cost of CNS progression was applied as a one-off cost on entering the PD health state.

Table 19 Progression management costs due to CNS metastases

Resource	Proportion of patients treated (company base case)	Unit cost	Source
Stereotactic radiosurgery	20%	£3,366	NHS National Cost Collection 2023/2024,[52] AA71A-B - Stereotactic Intracranial Radiosurgery, for Neoplasms or Other Neurological Conditions, with CC Score 0-4+
WBRT	25%	£5,200	Royal College of Radiologists 2019 (TA761[34])
Surgery (craniotomy)	0%	£12,235	NHS National Cost Collection 2023/2024,[52] Intracranial procedures for patients aged 19 years and over, weighted average (AA50A-C, AA51A-D, AA52A-D, AA53A-D, AA54A-C, AA55A-C, AA57A)
Steroids (dexamethasone)	100%	£189.89	NHS National Cost Collection 2022/23[56]: PHCD00066, PHCD00215, PHCD00271 – dexamethasone intraocular implant, intra-erythrocyte, intravitreal implant (weighted average), inflated to 2024 prices

CC=complication/comorbidity; CNS=central nervous system; CS=company submission; NHS=National Health Service; WBRT=whole brain radiotherapy
Source: CS, Table 60

Adverse event costs

Unit costs for Grade ≥3 AEs were sourced from the NHS Cost Collection 2023/24[52] (CS, Table 57). AE costs were calculated by multiplying AE incidence rates (by treatment) by unit costs; total costs were applied as one-off costs in the first model cycle.

End of life costs

The company applied a one-off terminal care cost of £12,411 on entry into the dead health state (inflated to 2024 prices[54]); healthcare resource use estimates were sourced from Brown 2023[57] and unit costs were sourced from the Personal Social Services Research Unit (PSSRU) 2023.[54]

4.2.9 Severity modifier

The company considered that, for this indication, treatment with osimertinib does not meet the criteria for a severity modifier.

5 COST EFFECTIVENESS RESULTS

5.1 Base case analysis

The cost effectiveness results presented in this section were generated by the company's clarification model; this model included a corrected radiotherapy cost and used electronic Market Information Tool (eMIT) prices for generic drugs (company response to clarification questions B6 and C3).

The company base case deterministic results are presented in Table 20. Company base case probabilistic sensitivity analysis (PSA) results (1,000 model iterations) are presented in Table 21.

Table 20 Company base case deterministic results (PAS price for osimertinib)

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
BSC	[redacted]	[redacted]	-	-	-
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,225

BSC=best supportive care; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: company response to clarification question C3, Table 5

Table 21 Company base case probabilistic results (PAS price for osimertinib)

Treatment	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
BSC	[redacted]	[redacted]	-	-	-
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	£17,878

BSC=best supportive care; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: company clarification model

5.2 Sensitivity analyses

The company varied parameter input values individually in deterministic sensitivity analyses (DSA). Upper and lower values were based on ±10% of the mean base case value or other plausible maximum and minimum values. Parameters with no associated uncertainty (e.g., drug costs) or that could not be varied independently (e.g., parametric model parameters) were excluded from the analyses. Cost effectiveness results were most sensitive to HSUVs, the proportion of patients in the BSC arm who received at least one line of subsequent treatment and the proportion of patients in the BSC arm who received osimertinib as a first subsequent treatment.

5.3 Scenario analyses

The company conducted scenario analyses (n=10) exploring alternative model assumptions and alternative parameter value estimates. Cost effectiveness results were most sensitive to

the removal of the 10-year TTD cap and using a lognormal distribution to model TTP and PFS in the osimertinib arm.

5.4 Validation

To verify model cost effectiveness results, internal validation was performed by an independent senior health economist. The validation process included:

- systematically checking individual formulae on a sheet-by-sheet basis
- cross checking input values against source references
- ensuring transformation and derivation of model input values were as described and had been conducted correctly
- testing functionality (including navigation, and any other macros) for errors
- a check of the PSA and DSA, including distributions used and rationales for distribution choices.

Model assumptions and parameter values were validated by clinical experts.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

The company submitted an economic model developed in Microsoft Excel to generate cost effectiveness results for the comparison of osimertinib versus BSC for patients with unresectable locally advanced EGFRm-positive NSCLC whose disease had not progressed during or after platinum-based CRT.

In response to clarification, the company provided an updated economic model that used eMIT prices for generic drugs and an updated radiotherapy cost (company response to clarification questions B6 and C3).

6.1 Overview of modelling issues identified by the EAG

The EAG reviewed the company model to check that calculations were accurate, and parameter values matched the values presented in the CS. The EAG has made the following minor corrections to errors in the company clarification model:

- used methods to calculate osimertinib drug administration and monitoring costs that are consistent with the calculation of osimertinib drug acquisition costs
- amended the model such that the first survival benefit is accrued in model cycle 1
- amended HCRU estimates in the PF and PD states to match those presented in CS, Table 55
- amended pemetrexed, docetaxel and carboplatin drug prices to match the prices listed in company clarification response, Table 3 and corrected afatinib drug acquisition cost
- assigned HCRU estimates lognormal distributions in the PSA so that only positive values were sampled.

The EAG has corrected the company clarification model; corrected company base case cost effectiveness results are presented in Table 29 (A2). Details of the EAG corrections are provided in Appendix 1, Section 8.1.

A summary of the EAG's critique of the company cost effectiveness analysis is presented in Table 22. Section 6.2 to Section 6.6 includes details of the EAG's major revisions to the EAG corrected company clarification model.

Table 22 Summary of EAG critique of company cost effectiveness model

Aspect considered	EAG comment	Section of EAG report
Model structure	The company model structure and time horizon are appropriate.	NA
Population	LAURA trial placebo arm PFS is lower than placebo arm PFS in other clinical trials for patients with locally advanced unresectable EGFRm-positive NSCLC. It is unclear whether LAURA trial placebo arm survival outcomes are generalisable to NHS clinical practice.	NA
Comparators	Clinical advice to the EAG is that durvalumab is not routinely prescribed to patients with unresectable locally advanced EGFRm NSCLC whose disease has not progressed during or after platinum-based CRT. The inclusion of BSC (active monitoring) as the only comparator in the company model is therefore appropriate.	NA
Overall survival	There is no statistically significant difference in OS between the LAURA trial osimertinib and placebo arms; at the 5 January 2024 DCO, most patients in the placebo arm had progressed and initiated osimertinib. **EAG revision:** alternative modelling of PPS for patients receiving BSC substantially reduces the OS gain for patients treated with osimertinib.	6.2.1
Post-progression survival	Mean survival in the PD health state for patients initially treated with BSC is substantially lower than the expected survival of TA654[39] patients treated with osimertinib. **EAG revision**: use the Weibull distribution to generate PPS estimates for patients initially treated with BSC. LAURA trial PPS data are uncertain. **EAG exploratory scenario**: the exponential distribution is used to generate PPS estimates for patients treated with osimertinib in an exploratory scenario.	6.2.1
Time to progression and progression-free survival	The company selected the Weibull distribution to generate TTP and PFS estimates for patients treated with osimertinib. It is uncertain whether the hazard of progression implied by the Weibull distribution represents the change in hazard observed in the LAURA trial osimertinib arm and produces clinically plausible long-term PFS estimates. **EAG exploratory scenario**: use the exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib.	6.3
Time to treatment discontinuation	The company generated osimertinib TTD estimates using LAURA trial K-M data up to 36 months and an exponential distribution thereafter. **EAG revision**: use the same distribution used to generate PFS and TTD estimates from the start of the model. The company assumed that no patients would remain on treatment with osimertinib after 10 years; this assumption was based on clinical advice[12] that patients were unlikely to remain on treatment indefinitely. **EAG revision**: remove the 10-year treatment stopping rule.	6.4

Aspect considered	EAG comment	Section of EAG report
Subsequent treatments	In the company model, i) the proportion of patients who received at least one subsequent treatment and ii) the proportion who received osimertinib as a first subsequent treatment were based on the average of clinical expert estimates. **EAG revision**: use estimates informed by LAURA trial data so that modelled costs and post-progression survival are aligned.	6.5
Utility values	The company PF utility value exceeds the general population utility value (age- and sex- matched to LAURA trial baseline characteristics). In addition, the company PD utility value does not reflect the decline in HRQoL that occurs as disease progresses. **EAG revisions**: set the PF utility value to the age- and sex-matched general population utility value and use the average of the TA654[39] PFS and PD utility values to represent HRQoL in the PD health state.	6.6
Drug costs	Two of the generic drug prices in the company clarification model do not match those listed in the company clarification response.	6.1
Healthcare resource use	Appropriate cost and resource use values were applied and supported by clinical advice.	NA
Adverse events	The approach to modelling AEs is appropriate. The inclusion of AE disutility values may result in double counting; however, their inclusion has a negligible impact on model QALYs.	NA
Company severity modifier	The EAG agrees with the company that a severity modifier should not be applied.	NA
PSA	The EAG has excluded drug administration and disease management unit costs from the PSA and used more appropriate distributions to sample values for HCRU parameters. Model PSA costs and QALYs results do not align with deterministic costs and QALYs; ICERs per QALY gained are similar.	6.1

AE=adverse event; BSC=best supportive care; CRT=chemoradiation; DCO=data cut-off; EAG=External Assessment Group; EGFRm=epidermal growth factor receptor mutation; HRQoL=health-related quality of life; HCRU=health care resource use; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; NA=not applicable; NHS=National Health Service; NSCLC=non-small cell lung cancer; OS=overall survival; PD=progressed disease; PF=progression-free; PFS=progression-free survival; PPS=post-progression survival; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year; TTD=time to treatment discontinuation; TTP=time to progression

6.2 Post-progression survival

The company has not directly generated OS estimates as they considered that LAURA trial OS data were too immature (CS, p91); instead, the company has generated OS estimates using PFS and PPS data. The EAG highlights that:

- only short-term LAURA trial PPS data are available, particularly for patients initially treated with osimertinib. LAURA trial median PPS follow-up is approximately 7.5 months for patients in the osimertinib arm and 22.5 months for patients in the placebo arm (CS, Table 14 and Table 16).
- analysis of 5 January 2024 DCO data showed that, among patients with progressed disease, 24/53 deaths had occurred in the osimertinib arm and 13/62 deaths had occurred in the placebo arm.
- patients whose disease progresses quickly may have a worse prognosis than patients who are currently progression-free but will experience disease progression in the future.[58] The EAG considers that the relative impact of any bias is likely to be larger for

company model patients treated with osimertinib than for patients treated with BSC as analyses of the 5 January 2024 DCO data showed that most LAURA trial placebo arm patients had progressed.

The EAG therefore considers that PPS estimates for patients treated with osimertinib and BSC are uncertain and highlights that changes to PPS have a large impact on cost effectiveness estimates.

6.2.1 BSC

In the company base case, the mean PPS for patients initially treated with BSC is [redacted] months. Mean PPS has been calculated using survival data from patients who received osimertinib as a subsequent treatment and survival data from patients who received other subsequent treatments. The EAG has deconstructed company base case mean PPS ([redacted] months) into the average time on osimertinib treatment (adjusted to [redacted] months to account for patients who do not receive osimertinib as subsequent treatment) and a residual survival time ([redacted] months). The residual survival is made up of a) for patients who received osimertinib as a subsequent treatment, survival post-subsequent osimertinib treatment and b) for patients who did not receive osimertinib as a subsequent treatment, total PPS. The EAG considers that, compared to NICE AC preferred TA654[39] OS estimates, the company has underestimated PPS for patients treated with BSC (Table 23).

Table 23 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)	
	Best supportive care (post-progression)	**Osimertinib (TA654[39])**
	Company base case	**NICE AC-preferred assumptions[a]**
Osimertinib treatment duration	[redacted][b]	21.96
Mean survival after discontinuing osimertinib (+ mean survival for patients who do not receive osimertinib)	[redacted]	34.19 to 38.26
Total survival	[redacted]	56.15 to 60.22

[a] Mean survival by health state was not reported for the committee-preferred assumptions therefore the EAG has adjusted the total undiscounted survival time (66.95 months) reported for the company base case using the ratio of discounted life years from the company base case to the relevant TA654[39] EAG scenarios (4.077/4.861 and 4.372/4.861). Since the committee preferred assumptions relate only to different treatment waning scenarios for OS, the EAG has assumed the mean PFS is unaffected.
[b] The average osimertinib treatment duration ([redacted] months) is adjusted to account for the proportion of patients who did not receive osimertinib after progression in company base case ([redacted]).
AC=appraisal committee; BSC=best supportive care; EAG=External Assessment Group; PD=progressed disease; PFS=progression-free survival
Source: company clarification model and TA654[39]

Data presented in Table 23 show that treatment duration with osimertinib is longer than in TA654;[39] however, mean survival after discontinuing treatment with osimertinib is much shorter than TA654[39] assumptions. Clinical experts[12] consulted by the company agreed that

treatment duration was likely to be longer for patients who received osimertinib after progression in the locally advanced unresectable setting compared to patients who received osimertinib when progression-free in the metastatic setting. Clinical advice to the EAG is that this is a reasonable assumption. However, for the BSC patient cohort entering the PD health state, average survival after discontinuing osimertinib (and survival for those who receive other subsequent treatments) is [redacted] months. The EAG highlights that [redacted] months is not in line with the expected survival of patients after progressing on osimertinib as a first-line treatment in the metastatic setting (34.19 to 38.26 months, Table 23).

The FLAURA trial,[48] which assessed the clinical effectiveness of osimertinib (versus gefitinib or erlotinib) as a treatment for patients with untreated EGFRm-positive advanced NSCLC, provided data that were used to inform TA654.[39] In this trial, 95% of patients had metastatic disease at baseline, whereas 44% (27/62; CS, Figure 12) of LAURA trial placebo arm patients were diagnosed with metastatic disease on progression. The EAG therefore considers that expected survival for patients who receive osimertinib as a first-line treatment in the metastatic setting is a lower bound for the expected survival of BSC patients in the PD health state.

The company selected the Gompertz distribution to generate PPS estimates for patients treated with BSC; the company considered that this distribution was a good statistical and visual fit to the LAURA trial K-M data, reflected the trend in the smoothed hazards observed in the LAURA trial and was considered plausible by three of the five clinicians consulted.[12] The EAG highlights that the Weibull distribution has a similar statistical fit to the Gompertz distribution (the difference in AIC and BIC scores is approximately [redacted] points) and was also considered plausible by three clinicians consulted by the company.[12] The EAG has revised the company model by using the Weibull distribution to generate PPS estimates for patients treated with BSC as the Weibull distribution generates PPS estimates that are more in line with TA654[39] model estimates than estimates generated by the Gompertz distribution (Table 23). A comparison of company, EAG and TA654 survival estimates for patients treated with osimertinib is presented in Table 24.

Table 24 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)			
	Best supportive care (post-progression)		Osimertinib (TA654[39])	
	Company base case (Gompertz)	EAG base case (Weibull)	Company base case	AC-preferred assumptions
Osimertinib treatment duration	[redacted][a]	[redacted][a]	21.96	21.96
Mean survival after discontinuing osimertinib (+ mean survival for patients who do not receive osimertinib)	[redacted]	[redacted]	44.99	34.19 to 38.26
Total survival	[redacted]	[redacted]	66.95	56.15 to 60.22

[a] Adjusted to account for the proportion of patients who did not receive osimertinib after progression
AC=appraisal committee; BSC=best supportive care; EAG=External Assessment Group; PD=progressed disease
Source: company clarification model and TA654[39]

6.2.2 Osimertinib

The company selected the Gompertz distribution to generate PPS estimates for patients treated with osimertinib; the company considered the Gompertz distribution was a good statistical fit to LAURA trial data, reflected the increase in hazard of post-progression death in the LAURA trial osimertinib arm and three of the five clinical experts consulted[12] agreed that it generated the most clinically plausible estimates. The statistical goodness of fit of the exponential, Weibull, Gompertz, gamma and generalised gamma distributions were very similar (CS, Table 35). Two clinicians considered the lognormal distribution could generate reasonable PPS estimates while a third clinician considered most patients initially treated with osimertinib would die quickly upon progression.[12] The EAG highlights that there is no external clinical effectiveness data available to validate long-term survival estimates for patients treated with osimertinib in the locally advanced unresectable setting whose disease progresses, and therefore all PPS estimates are uncertain.

In the company base case, mean survival in the PD state for patients initially treated with osimertinib is [redacted] months which is lower than the expected survival after progression on osimertinib for patients initially treated with BSC ([redacted] months) in the EAG base case. The EAG therefore considers that company PPS estimates for patients treated with osimertinib may be pessimistic. In an exploratory scenario, the EAG has used the exponential distribution to generate PPS estimates for patients treated with osimertinib; mean survival in the PD state increases to [redacted] months. The EAG highlights that patients initially treated with osimertinib progress at a later timepoint (and are therefore older) than patients initially treated with BSC who progress on osimertinib as a subsequent treatment. Conversely, patients initially treated with osimertinib will have less advanced disease on progression than patients initially treated with BSC who progress on osimertinib as a subsequent treatment. It is therefore unclear

whether survival after progression on osimertinib would be similar between the two patient cohorts.

6.3 Time to progression and progression-free survival

The company selected the same distributions (osimertinib: Weibull; BSC: generalised gamma) to generate TTP and PFS estimates; this approach was taken to prevent illogical crossing of curves and was an approach that was supported by the clinical experts consulted by the company.[12] The EAG agrees with the company that using the same distribution to model both endpoints is a reasonable approach. The EAG also agrees with the company that the generalised gamma distribution is the most appropriate distribution to use to generate TTP and PFS estimates for patients receiving BSC; this distribution had the best statistical fit to LAURA trial K-M data (other model selection criteria are less relevant when data are mature).

The EAG highlighted (clarification question B1) that none of the distributions fitted by the company appear to reflect the change in the LAURA trial osimertinib arm hazard of progression and that only the exponential distribution generated a 10-year PFS rate (11.5%) that was within the range suggested by clinical experts (10% to 15%).[12] In response, the company fitted more flexible parametric distributions but noted that all these additional distributions generated 10-year PFS estimates that were substantially above the 10-year estimate generated by the Weibull distribution (18.8%) and that using any of the alternative distributions generated estimates that were clinically implausible; the EAG agrees with the company.

Clinical experts consulted by the company[12] did not agree on the range of plausible long-term PFS estimates; in one-to-one interviews, four of the five clinical experts considered the Weibull distribution generated the most plausible long-term estimates (CS, p102) despite a 10-year PFS estimate that was above the range suggested by clinicians at a group advisory board.[12] The LAURA trial osimertinib arm hazard of progression appears to increase after 28 months (CS, Figure 19); however, CIs were not plotted and a low number of patients were at risk beyond 36 months (n=28). It is not clear whether the initial decrease and flattening of the progression hazard implied by the Weibull distribution is plausible as resistance to osimertinib can develop over time.[59] Longer term LAURA trial data are needed to inform how the shape of the hazard changes over time and help assess the plausibility of different long-term TTP/PFS estimates.

The EAG has generated cost effectiveness results using the exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib; this is an exploratory scenario to evaluate the impact of using the most pessimistic of the seven standard

distributions considered by the company. LAURA trial, Weibull distribution and exponential distribution PFS rates for patients treated with osimertinib are presented in Table 25.

Table 25 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%

[a] Only one patient at risk therefore K-M estimate may be unreliable
AIC=Akaike information criterion; BIC=Bayesian information criterion; K-M=Kaplan-Meier
Source: CS, Table 33

6.4 Time to treatment discontinuation: osimertinib

The company adopted a piecewise approach to generate time to treatment discontinuation (TTD) estimates for patients treated with osimertinib; LAURA trial K-M data were used up to 36 months and an exponential distribution was used to generate TTD estimates for the remainder of the model time horizon. The company justification for the choice of the 36 months timepoint was that, at this time point, a small number of LAURA trial patients remained at risk (CS, p117). In response to clarification question B2, the company explained that none of the single distributions considered had a good (statistical) fit and generated clinically plausible estimates. Although the exponential distribution has a relatively poor statistical fit (AIC rank: [redacted], BIC rank: [redacted]), company clinical experts considered the distribution was the most plausible for UK clinical practice (company response to clarification question B2). However, the EAG was unable to identify information in the company advisory board notes[12] that supported the use of the exponential distribution.

The company piecewise approach to generating TTD estimates results in a sustained separation of the PFS and TTD curves after 36 months (

Figure 2); this phenomenon is not supported by LAURA trial PFS and TTD K-M data, nor is it consistent with a treat-to-progression regimen. The EAG considers that it was not necessary to use a piecewise approach and has generated TTD estimates using the Weibull distribution; this is the same distribution that the company selected to generate PFS (and TTP) estimates. When using the Weibull distribution to generate TTD estimates, the osimertinib TTD curve lies slightly above the PFS curve after 10 years; however, in the company model osimertinib drug acquisition costs are calculated using the minimum of PFS and TTD estimates. In the company and EAG alternative base case, TTD estimates are therefore effectively capped by the PFS curve.

The company has assumed that no patients remain on treatment with osimertinib after 10 years; this assumption was based on clinical advice[12] that patients were unlikely to remain on treatment indefinitely (some clinicians suggested patients may discontinue treatment after 3 to 5 years of being progression free). In the company base case, at 10 years [redacted] of patients treated with osimertinib are expected to be progression-free and [redacted] of patients are expected to still be receiving osimertinib treatment. The EAG notes that neither the expected EMA licence[9] (CS, Table 2) nor the LAURA trial protocol[25] includes a treatment stopping rule; in the LAURA trial, osimertinib is administered as a treat-to-progression regimen. Imposing a treatment stopping rule is likely to require modelling of treatment waning and the possibility of osimertinib retreatment.

The EAG considers that it is appropriate to remove the 10-year osimertinib treatment stopping rule (in line with company scenario analysis; CS, Table 69).

Figure 2 Company and EAG base case osimertinib PFS and TTD[a]

[a] K-M data presented up to 36 months
EAG=External Assessment Group; K-M=Kaplan-Meier; PFS=progression-free survival; TTD=time to treatment discontinuation
Source: company clarification model

6.5 Proportion of patients receiving subsequent treatment

6.5.1 BSC

In the company model, [redacted] of patients treated with BSC are assumed to receive at least one line of subsequent treatment on progression. Of these patients, [redacted] are assumed to receive osimertinib as their first subsequent treatment. These two estimates are the average of estimates provided by company clinical experts.[12] The product of these two estimates ([redacted]) is lower than the proportion of LAURA trial placebo arm patients who progressed and received osimertinib as their first subsequent treatment (50/62=80.6%; CS, p51). The company considered that clinical expert estimates were more representative of UK clinical practice than LAURA trial data.

6.5.2 Osimertinib

The EAG highlights that the proportion of patients in the company model who are initially treated with osimertinib and who progress and receive at least one line of subsequent treatment ([redacted]) is also lower than the proportion of LAURA trial osimertinib arm patients who received at least one line of subsequent treatment (42/53=79.3%; CS, p37 and CS, Table 14). As rechallenge with osimertinib is unlikely for NHS patients, the company model did not include osimertinib as a subsequent treatment for patients initially treated with osimertinib. In the LAURA trial, 28 patients received an EGFR-TKI after discontinuing treatment with osimertinib (CS, Table 12). The EAG highlights that it is not known i) how many of these patients had discontinued osimertinib due to toxicity or progression or, ii) the length of time these patients were treated with an EGFR-TKI.

6.5.3 EAG revision

The EAG has revised the company model by using LAURA trial data to estimate proportions of patients receiving subsequent treatments; this approach means that modelled costs and PPS estimates are aligned (Table 26).

Table 26 Proportions of model patients receiving first subsequent treatment on progression

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%

BSC=best supportive care; CS=company submission; EAG=External Assessment Group
Source: CS, Table 11 and Table 48

6.6 Health state utility values

The company model HSUVs are presented in Table 27. The EAG considers that the company HSUVs lack face validity as:

- the PF HSUV ([redacted]) exceeds the general population age- and sex-matched utility value (0.831)
- the PD HSUV value (0.794) does not reflect the decline in HRQoL as disease progresses.

In response to clarification question B4, the company stated that the Nafees[60] utility value (0.84) was comparable to the utility values used in the company model to represent HRQoL in the PF and PD health states. The EAG considers that the Nafees study[60] utility value has limited relevance as it does not reflect HRQoL reported directly by patients.

The EAG has revised the company model by setting the PF HSUV equal to the general population age- and sex-matched utility value (based on LAURA trial baseline age and sex, Table 13). The EAG considers that the company model should include at least two post-progression health states to enable a more accurate modelling of changes to patient HRQoL as disease progresses. Given the immaturity of LAURA trial PPS data, the EAG acknowledges that this would likely necessitate using external data to inform the length of time spent in each post-progression health state; however, external data may not be generalisable to patients initially treated with osimertinib for locally advanced unresectable EGFRm-positive NSCLC.

The EAG has generated cost effectiveness results using the average of the PF and PD utility values accepted by the TA654[39] NICE Appraisal Committee (Table 27). The EAG's preferred PF utility value may still overestimate patient HRQoL as patients who are asymptomatic may suffer from anxiety due to the fear of disease progression.

Table 27 Company and EAG health state utility values

Health state	Company base case		EAG revision	
	Value	Source	Value	Source
PF	[redacted]	LAURA trial EQ-5D-5L data mapped to EQ-5D-3L	0.831	Age-and sex matched general population value (LAURA trial baseline age and sex values)
PD	0.794	FLAURA trial PF utility value used in TA654[39]	0.725	Average of PF (0.794) and PD (0.704, 0.678) utility values used in TA654[39]

EAG=External Assessment Group; EQ-5D-3L=EuroQol-5 Dimensions-3 Levels; EQ-5D-5L=EuroQol-5Dimensions-5 Levels; PD=progressed disease; PF=progression free
Source: company clarification model and TA654[39]

6.7 Impact of EAG revisions on company base case cost effectiveness results

The EAG has made the following revisions to the EAG corrected company base case cost effectiveness analysis:

- Weibull distribution to generate PPS estimates for patients receiving BSC (R1)
- osimertinib TTD estimates generated using the same distribution selected for PFS (R2)
- removal of 10-year osimertinib treatment stopping rule (R3)
- subsequent treatment proportions informed by LAURA trial (R4)
- set PF utility value to age- and sex-matched general population utility value (R5)
- PD value: average of TA654[39] HSUVs (R6)

The EAG has carried out an exploratory analysis to assess the impact on model outcomes of using an:

- exponential distribution to generate PPS estimates for patients treated with osimertinib (S1)
- exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib (S2)

Details of EAG revisions to the company model are presented in Section 8.1 of this EAG report. Deterministic and probabilistic results are presented in Table 29 and Table 30, respectively. All results presented in this report have been generated using list prices except for osimertinib (PAS price for this indication and CAA price for metastatic setting). Cost effectiveness results generated using available confidential drug prices (Table 28) are available in a confidential appendix.

Table 28 Pricing sources used in a confidential appendix

Treatment	Price source/type of commercial arrangement
Osimertinib (this submission)	Simple PAS discount
Osimertinib (TA654[39])	CAA price
Docetaxel	eMIT price
Paclitaxel	eMIT price
Pemetrexed	MPSC prices
Carboplatin	eMIT price
Atezolizumab	CAA price
Bevacizumab	MPSC prices
Afatinib	Simple PAS discount
Gefitinib	eMIT price

CAA=Commercial Access Agreement; eMIT=electronic Market Information Tool; MPSC=Medicines Procurement Supply Chain; PAS=Patient Access Scheme

Table 29 Deterministic cost effectiveness results: osimertinib versus best supportive care (osimertinib PAS and CAA prices)

Scenario/EAG revisions	Osimertinib		BSC		Incremental		ICER (£/QALY)	Change from base case (A2)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Clarification company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,225**	**-**
A2. EAG corrected company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,090**	**-**
R1) Weibull distribution to generate PPS estimates for patients receiving BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,360	£19,270
R2) Osimertinib TTD estimates generated using the same distribution selected for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,628	£5,538
R3) Removal of 10-year osimertinib treatment stopping rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,519	£4,429
R4) Subsequent treatment proportions informed by LAURA trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,543	-£2,547
R5) Set PF utility value to age and sex-matched general population utility value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,999	£1,909
R6) PD value: average of TA654[39] HSUVs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,999	-£1,090
B. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£68,602**	**£49,512**
S1) Exponential distribution to generate PPS estimates for patients treated with osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,477	-£2,613
S2) Exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,611	£6,521
C1. B+S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,444**	**£29,354**
C2. B+S1+S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£50,291**	**£31,201**

BSC=best supportive care; CAA=Commercial Access Agreement; EAG=External Assessment Group; HSUVs=health state utility values; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PD=progressed disease; PF=progression-free; PFS=progression-free survival; PPS=post-progression survival; QALYs=quality adjusted life year; TTD=time to treatment discontinuation; TTP=time to progression

Table 30 Probabilistic cost effectiveness results: osimertinib versus best supportive care (osimertinib PAS and CAA prices)

Scenario/EAG revisions	Osimertinib		BSC		Incremental		ICER (£/QALY)	Change from base case (A2)
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Clarification company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,878**	**-**
A2. EAG corrected company clarification base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£18,940**	**-**
B. EAG alternative base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£64,239**	**£45,299**

BSC=best supportive care; CAA=Commercial Access Agreement; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

6.8 Cost effectiveness conclusions

The EAG considers that PPS estimates and the magnitude of the OS benefit for patients treated with osimertinib are uncertain. The majority of patients initially treated with BSC receive osimertinib on progression; the EAG considers that it is likely that, compared to the expected survival of patients who received osimertinib in TA654,[39] PPS for patients initially treated with BSC has been underestimated by the company.

PPS for patients initially treated with osimertinib is associated with greater uncertainty than PPS for patients initially treated with BSC; there is a lack of relevant external evidence available to validate long-term survival estimates for patients initially treated with osimertinib.

Company and EAG cost effectiveness results are sensitive to the choice of distribution used to estimate osimertinib TTD and the inclusion of an osimertinib treatment stopping rule.

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8 APPENDICES

8.1 EAG revisions to the company model

EAG revisions	Implementation instructions
C1) Osimertinib cost corrections	**Insert sheet named 'EAG Revisions'** In cell C3 enter text "C1" Name cell D3 "EAG_C1" Set value in cell D3 =1 In Sheet 'Flow' Set value in cell AA14 =IF($B14>$AN$9,0,IF(EAG_C1=1,MIN(H14,I14),$H13)*$AA$9*(CHOOSE(discount_option, $D14, 1))) Copy formula in cell AA14 to range AA14:AA484 Set value in cell AB14 =IF($B14>$AN$9,0,$AB$9*(CHOOSE(discount_option, $D14, 1)))*IF(EAG_C1=1,MIN(H14,I14),cohort) Copy formula in cell AB14 to range AB14:AB484
C2) Survival gain in model cycle 0 correction	In Sheet 'EAG Revisions' In cell C4 enter text "C2" Name cell D4 "EAG_C2" Set value in cell D4 =1 In Sheet 'Flow' Set value in cell I13 =IF(EAG_C2=1,0,'Surv_calcs (STM)'!BF22) Copy formula in cell I13 to range I13:K13 Set value in cell Q13 =IF(EAG_C2=1,0,'Surv_calcs (STM)'!BV22) Copy formula in cell Q13 to range Q13:S13 Set value in cell I14 =IF(EAG_C2=1,'Surv_calcs (STM)'!BF22,'Surv_calcs (STM)'!BF23) Copy formula in cell I14 to range I14:K484 Set value in cell Q14 =IF(EAG_C2=1,'Surv_calcs (STM)'!BV22,'Surv_calcs (STM)'!BV23) Copy formula in cell Q14 to range Q14:S484

C3) HCRU estimates correction	In Sheet 'EAG Revisions' In cell C5 enter text "C3" Name cell D5 "EAG_C3" Set value in cell D5 =1 In Sheet 'Costs_DM' Set value in cell D19 =IF(EAG_C3=1,3.65,3.4) Set value in cell D20 =IF(EAG_C3=1,3.53,3.28) Set value in cell D21 =IF(EAG_C3=1,3.05,2.8) Set value in cell E37 =IF(EAG_C3=1,3.56,4.39) Set value in cell E38 =IF(EAG_C3=1,2.57,3.486) In Sheet '_Parameters' Set value in cell A501=IF(EAG_C3=1,3.65,3.4) Set value in cell A502 =IF(EAG_C3=1,3.53,3.28) Set value in cell A503 =IF(EAG_C3=1,3.05,2.8) Set value in cell A541 =IF(EAG_C3=1,3.56,4.39) Set value in cell A542=IF(EAG_C3=1,2.57,3.486)
C4) Drug price corrections	In Sheet 'EAG Revisions' In cell C6 enter text "C4" Name cell D6 "EAG_C4" Set value in cell D6 =1 In Sheet 'Costs_SubTx' Set value in cell P56 =IF(EAG_C4=1,38.93,232.64) Set value in cell N55 =IF(EAG_C4=1,500,150) Set value in cell P55 =IF(EAG_C4=1,114.44,12.18) Set value in cell N53 =IF(EAG_C4=1,160,20) Set value in cell K61 =IF(EAG_C4=1,28,21) Set value in cell T61 =Costs_SubTx!P61*Costs_SubTx!O61*IF(EAG_C4=1,1,Costs_SubTx!AI61) In Sheet 'Parameters' Set value in cell A408 =IF(EAG_C4=1,500,150) Set value in cell A410 =IF(EAG_C4=1,114.44,12.18) Set value in cell A422 =IF(EAG_C4=1,38.93,232.64) Set value in cell A384 =IF(EAG_C4=1,160,20) Set value in cell A477 =IF(EAG_C4=1,28,21)

C5) PSA corrections	In Sheet 'EAG Revisions' In cell C7 enter text "C5" Name cell D7 "EAG_C5" Set value in cell D7 =1 In Sheet '_Parameters' Remove data validation from ranges Q367:Q376, Q519:Q529, Q550:Q559, Q580:Q591, Q600:Q626, Q649:Q654 Set value in cell Q367 =IF(EAG_C5=1,"No","Yes") Copy formula in cell Q367 to ranges Q367:Q376, Q519:Q529, Q550:Q559, Q580:Q591, Q600:Q626, Q649:Q654 Remove data validation from ranges U497:U518, U530:U549, U564:U579, U592:U599 Set value in cell U497 =IF(EAG_C5=1,"Lognormal","Normal") Copy formula in cell to ranges U497:U518, U530:U549, U564:U579, U592:U599 Set value in cell T508 =IF(EAG_C5=1,($S508-$R508)/(2*NORMINV(0.975,0,1)),Costs_DM!G13) Copy formula in cell T508 to cell T509
R1) Weibull distribution to generate PPS estimates for patients receiving BSC	In Sheet 'EAG Revisions' In cell C9 enter text "R1" Name cell D9 "EAG_R1" Set value in cell D9 =1 In Sheet 'Survival_STM' Clear data validation from cell AA49 Set value in cell AA49 =IF(EAG_R1=1,"Weibull","Gompertz") In Sheet '_Parameters' Set value in cell A709 =IF(EAG_R1=1,"Weibull","Gompertz")
R2) Osimertinib TTD estimates generated using the same distribution selected for PFS	In Sheet 'EAG Revisions' In cell C10 enter text "R2" Name cell D10 "EAG_R2" Set value in cell D10 =1 In Sheet 'Survival_TTD' Clear data validation from cell L17 Set value in cell L17 =IF(EAG_R2=1,Int_STM_PF_PD_distribution,"Exponential") Set value in cell M32 =IF(EAG_R2=1,0,36) In Sheet '_Parameters' Set value in cell A311=IF(EAG_R2=1,0,36)

R3) Removal of 10-year osimertinib TTD cap	In Sheet 'EAG Revisions' In cell C11 enter text "R3" Name cell D11 "EAG_R3" Set value in cell D11 =1 In Sheet 'Survival_TTD' Set value in cell M34 =IF(EAG_R3=1,time_horizon_cycles,120) In Sheet '_Parameters' Set value in cell A312 =IF(EAG_R3=1,time_horizon_cycles,120)
R4) Subsequent treatment proportions informed by LAURA trial	In Sheet 'EAG Revisions' In cell C12 enter text "R4" Name cell D12 "EAG_R4" Set value in cell D12 =1 In Sheet 'Costs_SubTx' Set value in cell F12 =IF(EAG_R4=1,42/53,67%) Set value in cell F13 =IF(EAG_R4=1,57/62,86%) Set value in cell J38 =IF(EAG_R4=1,50/57,0.847103116502824) In Sheet '_Parameters' Set value in cell A313 =IF(EAG_R4=1,42/53,0.67) Set value in cell A314 =IF(EAG_R4=1,57/62,0.86) Set value in cell A336 =IF(EAG_R4=1,50/57,0.847103116502824)
R5) Set PF utility value to age- and sex-matched general population utility value	In Sheet 'EAG Revisions' In cell C13 enter text "R5" Name cell D13 "EAG_R5" Set value in cell D13 =1 In Sheet 'Utilities' Set value in cell F13 =IF(EAG_R5=1,'Gen Pop Mortality & Utility'!N73,0.878) In Sheet '_Parameters' Set value in cell A655 =IF(EAG_R5=1,'Gen Pop Mortality & Utility'!N73,0.878)
R6) PD value: average of TA654[39] HSUVs	In Sheet 'EAG Revisions' In cell C14 enter text "R6" Name cell D14 "EAG_R6" Set value in cell D14 =1 In Sheet 'Utilities' Set value in cell F14 =IF(EAG_R6=1,(0.794+0.704+0.678)/3,0.794) In Sheet '_Parameters' Set value in cell A656 =IF(EAG_R6=1,(0.794+0.704+0.678)/3,0.794)

S1) Exponential distribution used to generate PPS estimates for patients treated with osimertinib	In Sheet 'EAG Revisions' In cell C16 enter text "S1" Name cell D16 "EAG_S1" Set value in cell D16 =1 In Sheet 'Survival_STM' Clear data validation from cell L49 Set value in cell L49 =IF(EAG_S1=1,"Exponential","Gompertz") In Sheet '_Parameters' Set value in cell A708 =IF(EAG_S1=1,"Exponential","Gompertz")
S2) Exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib	In Sheet 'EAG Revisions' In cell C17 enter text "S2" Name cell D17 "EAG_S2" Set value in cell D17 =1 In Sheet 'Survival_STM' Clear data validation from cell L18 Set value in cell L18 =IF(EAG_S2=1,"Exponential","Weibull") In Sheet '_Parameters' Set value in cell A706 =IF(EAG_S2=1,"Exponential","Weibull")

BSC=best supportive care; EAG=External Assessment Group; HCRU=health care resource use; HSUV=health state utility value; PD=progressed disease; PF=progression-free; PFS=progression-free survival; PPS=post-progression survival; PSA=probabilistic sensitivity analysis; TTD=time to treatment discontinuation; TTP=time to progression

EAG REVIEW OF UPDATED LAURA TRIAL OS DATA

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223] - EAG review of updated LAURA trial OS data

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR172246

Completed 25 April 2025

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1.1 Introduction

The cost effectiveness estimates presented in the CS were informed by LAURA trial data (5 January 2024) from the progression-free survival (PFS) analysis (primary outcome). January 2024 overall survival (OS) data were immature (19.9%) and demonstrated a non-statistically significant survival benefit for patients treated with osimertinib compared to those treated with placebo (hazard ratio [HR]=0.81, 95% confidence interval [CI]: 0.42 to 1.56). Following submission of the EAG report, the company provided 29 November 2024 LAURA trial OS data (31% maturity); these data suggest an improvement in OS benefit for patients treated with osimertinib compared to patient treated with placebo (HR=0.67, 95% CI: 0.40 to 1.14). The National Institute for Health and Care Excellence (NICE) asked the External Assessment Group (EAG) to review the data and comment on the impact of the updated data on company and EAG cost effectiveness results.

The EAG requested LAURA trial (29 November 2024) subsequent treatment data (see Section 1.3); the company was unable to provide these data as the data lock only captured OS data. Without these data, it is difficult to explain the change in LAURA trial OS Kaplan-Meier (K-M) data between January 2024 and November 2024; or to verify whether the subsequent treatment assumptions made in the company model are consistent with the November 2024 data. The EAG therefore considers that, in isolation, the November 2024 OS data has limited use for validating company or EAG cost effectiveness results.

1.2 Validation of company base case OS estimates

The company considers (company addendum, p1) that the November 2024 LAURA trial OS data support the company base case modelling assumptions as the modelled OS for patients treated with osimertinib is a good visual fit to LAURA trial osimertinib OS K-M data whilst overpredicting OS for patients receiving best supportive care (BSC).

The company model uses January 2024 LAURA trial data; OS is estimated using three endpoints (time to progression, PFS and post-progression survival [PPS]). The changes in LAURA trial OS data (both arms) between January 2024 and November 2024 is due to changes in one or more of these endpoints and/or subsequent treatments; the magnitude of these changes and their impact on both company and EAG modelled OS and cost effectiveness results is unknown.

1.3 Subsequent osimertinib treatment duration

1.3.1 LAURA trial placebo arm

LAURA trial (January 2024) mean osimertinib treatment duration for placebo arm patients who received osimertinib as a subsequent treatment ([redacted] months; company response to clarification question B5) is lower than the value used in the company model ([redacted] months); the company considered that LAURA trial data were too immature to use in the economic model (company submission [CS], p91) and this was accepted by the EAG.

The EAG highlights that subsequent treatment costs account for [redacted] of the total cost for patients treated with BSC; cost effectiveness results are therefore highly sensitive to mean osimertinib treatment duration. In addition, mean osimertinib treatment duration was used by the EAG to inform expected PPS for patients treated with BSC in the EAG alternative base case.

The EAG asked the company to provide LAURA trial (November 2024) mean osimertinib treatment duration for placebo arm patients who received osimertinib as a subsequent treatment. However, the company was not able to provide this information as this outcome was not part of the November 2024 DDO analysis plan. Therefore, it is not known if the mean osimertinib treatment duration for patients in the company model who are treated with BSC is consistent with November 2024 LAURA trial data. This also means that the EAG is not able to adjust PPS in line with November 2024 LAURA trial data.

1.3.2 LAURA trial osimertinib arm

Analysis of January 2024 LAURA trial data showed that 15/63 (23.8%) of osimertinib arm patients who discontinued osimertinib received osimertinib as a subsequent treatment (CS, Table 11). Analysis of November 2024 data showed that this proportion had increased to 29.7% (22/74).[1] Osimertinib rechallenge is not permitted in NHS clinical practice and the costs of subsequent osimertinib treatment have not been included in the model for patients treated with osimertinib. The EAG is concerned that patients who receive osimertinib (or other epidermal growth factor receptor tyrosine kinase inhibitors [EGFR-TKIs]) as a subsequent treatment may be deriving some clinical benefit that would not occur for NHS patients. The company was unable to provide data showing i) the length of time patients were treated with osimertinib as a subsequent treatment or ii) how many patients had discontinued osimertinib due to toxicity or progression (and received osimertinib as subsequent treatment).

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Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 31 March 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 **Comparisons made between LAURA and FLAURA**

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 60-61 The EAG has performed a comparison between TA654 OS estimates and the PPS for patients treated with BSC in LAURA. This problem relates to this text and the calculations performed in Table 23 and Table 24. If comparisons are to be performed text should be provided, giving context on the differences in populations and the differences in treatments received when assessing these data sources. Without this context, inaccurate conclusions risk being made.	*Please can the EAG add context on the differences in populations and differences in treatments received before the tables.* *For Table 23 and 24 - it is not clear that total survival reflects a proportion of patients not receiving osimertinib.* *For Table 23 and 24– Could the EAG clarify how mean survival after discontinuing osimertinib (+ mean survival for patients who do not receive osimertinib) was calculated?*	When making comparisons in the absolute outcomes between modelled TA654 (FLAURA) OS and PPS in the BSC arm in LAURA, the EAG has not appropriately considered or accounted for differences in the populations and differences in the treatments received in both arms.[1,2] **Differences in populations** Not all patients in the FLAURA trial, which informed TA654, had received CRT. This contrasts with patients in the LAURA trial. **Differences in treatments received** In LAURA, around 20% of all placebo patients did not receive osimertinib following progression and received	The EAG has added the following text to EAR, p60: “In the company base case, mean PPS for patients initially treated with BSC is [redacted] months. Mean PPS has been calculated using survival data from patients who received osimertinib as a subsequent treatment and survival data from patients who received other subsequent treatments. The EAG has deconstructed company base case mean PPS ([redacted] months) into the average time on osimertinib treatment (adjusted to [redacted] months to account for patients who do not receive osimertinib as

		less efficacious treatments. This is not accounted for in the comparison between 'total survival' in the EAG tables 23 and 24.	subsequent treatment) and a residual survival time ([redacted] months). The residual survival is made up of a) for patients who received osimertinib as a subsequent treatment, survival post-subsequent osimertinib treatment and b) for patients who did not receive osimertinib as a subsequent treatment, total PPS." **Differences in population** It is not clear why prior CRT would impact a comparison of FLAURA trial and LAURA trial survival estimates.
Pg 60-61 "The EAG has revised the company model by using the Weibull distribution to generate PPS estimates for patients treated with BSC as the Weibull distribution	*We suggest removing this scenario from consideration or considering the clinical plausibility of the two OS curves.* *Alternatively, the EAG should comment on the plausibility of the modelled OS vs. observed OS.*	The EAG does not assess the impact of this assumption on the modelled OS vs. the observed OS from the LAURA trial. This comparison has been provided in a plot in the Appendix (Figure 1) and shows a poor fit between the	The EAG does not consider that it is appropriate to assess the plausibility of modelled survival using the tail of the K-M curve as K-M estimates are unreliable when there are low

generates PPS estimates that are more in line with TA654".		modelling BSC OS and the LAURA placebo OS.[2]	numbers of patients are at risk. In the LAURA trial, only 15 patients in the placebo arm and 37 patients in the osimertinib arm are at risk of death at 39 months (CS, Figure 9). No changes made.
Pg 62 "Conversely, patients initially treated with osimertinib will have less advanced disease on progression than patients initially treated with BSC who progress on osimertinib as a subsequent treatment."	"Conversely, patients initially treated with osimertinib will have less advanced disease on progression than patients initially treated with BSC who progress on osimertinib as a subsequent treatment, *as reported in the LAURA trial*."	Evidence from the LAURA trial can be used to support this statement; 16% of patients progressed to distant metastases in the osimertinib arm compared to 37% in the placebo arm.[2]	Patients initially treated with BSC who receive osimertinib as a subsequent treatment and then progress will have experienced two disease progressions whereas patients initially treated with osimertinib will have had experienced one disease progression. The evidence from the LAURA trial referenced by the company is therefore not relevant to the statement. No changes made.

Issue 2 Missing argumentation to support clinically dubious assumptions

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 63: "The EAG has generated cost effectiveness results using the exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib; this is an exploratory scenario to evaluate the impact of using the most pessimistic of the seven standard distributions considered by the company."	*We suggest removing this scenario or considering the clinical plausibility of the two OS curves crossing. The company have further data to support this and have raised this with NICE.*	When the assumption of a constant hazard for osimertinib PFS and TTP is applied it results in the OS curves crossing for osimertinib and BSC (plot provided in Figure 2 in the Appendix). The EAG did not consider the clinical plausibility of this in the report.	The EAG has removed scenario C2 from EAR Table B and Table 29.

Issue 3 Incorrect statement about what the observed data can demonstrate

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 64: "The company piecewise approach to generating TTD	"The company piecewise approach to generating TTD estimates results in a sustained separation of the PFS and TTD curves after 36 months (Figure 2);	The TTD KM data does support the model selection made in the Company base case. Furthermore, the	This is not a factual inaccuracy. No changes made.

estimates results in a sustained separation of the PFS and TTD curves after 36 months (Figure 2); this phenomenon is not supported by LAURA trial PFS and TTD K-M data, nor is it consistent with a treat-to-progression regimen."	this phenomenon is not ~~supported by LAURA trial PFS and TTD K-M data, nor is it~~ consistent with a treat-to-progression regimen."	Company modelled TTD to align with clinical opinion from experts who have experience in treating patients using osimertinib. The EAG has chosen an assumption which means that patients will continue treatment in the very long run despite the clinical evidence provided, and this view is also not supported by TTD KM data.	

Issue 4 Company rationale for deviating from trial data not specified

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 65 "In the company model, 86% of patients treated with BSC are assumed to receive at least one line of subsequent treatment on progression. Of these patients, 84.7% are assumed to receive osimertinib as their first subsequent treatment.	"… The product of these two estimates (72.9%) is lower than the proportion of LAURA trial placebo arm patients who progressed and received osimertinib as their first subsequent treatment (50/62=80.6%; CS, p51*), but was considered to be more representative of UK clinical practice*."	Detail missing on why the Company considered it justified to deviate from the clinical trial	The EAR text has been amended as follows: "The company considered that clinical expert estimates were more representative of UK clinical practice than LAURA trial data."

These two estimates are the average of estimates provided by company clinical experts. The product of these two estimates (72.9%) is lower than the proportion of LAURA trial placebo arm patients who progressed and received osimertinib as their first subsequent treatment (50/62=80.6%; CS, p51)."			

Issue 5 Modelling errors introduced with corrections

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 57 "amended the model such that the first survival benefit is accrued in model cycle 1" This amendment has led to an inconsistent approach in modelling.	*The model should not begin with 0 distribution across health states. The EAG should either adopt the original modelling approach, or apply the half-cycle correction from cycle 0, if this is what was intended.*	Treatment acquisition, administration, AE costs and costs associated with CNS mets due to progression are all applied when no one is in the progression-free state. AE disutilities are also applied, leading to negative total QALYs in cycle 0.	The EAG correction removed the survival gain in model cycle 0 as, in the company base case, at 1 year, life years gained exceeded 12 months (progressions/deaths also occur at time 0). Half-cycle corrected health state membership distributions are applied

			in model cycle 1; this accounts for the distributions at the start of the model (i.e., where all patients are progression-free). Costs associated with CNS progression should be applied from model cycle 1; correcting this error reduces the company base case ICER per QALY gained by £4. The EAG has therefore not made any changes to the EAG correction.

Issue 6 Description of probabilistic results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 59 “Model PSA costs and QALYs results do not align with deterministic costs and	“Model PSA costs and QALYs results *broadly* ~~*do not*~~ align with deterministic costs and QALYs; ICERs per QALY gained are similar.”	It is inaccurate to say they do not align.	This is not a factual inaccuracy. No change made.

QALYs; ICERs per QALY gained are similar.”			

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6223 osimertinib Final EAG report 19032025 IC [CON], Page			
ID6223 osimertinib Final EAG report 19032025 IC [CON], Page 53	Treatment duration of osimertinib for patients initially treated with BSC	Subsequent treatment durations were sourced from the literature and validated by clinical experts (CS, Table 49). To inform the treatment duration of osimertinib for patients initially treated with BSC, the company used the [redacted].[50] Clinical experts[12] considered that patients in the placebo arm of the LAURA trial who receive osimertinib post-progression would have a longer mean treatment duration than	The EAG has amended the confidential marking as suggested.

		patients who received osimertinib as a first-line treatment in the metastatic setting. The company therefore increased the modelled mean osimertinib treatment duration from the [redacted].	

References

1. National Institute for Health and Care Excellence. Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer. 2020. Available from: https://www.nice.org.uk/guidance/ta654. Accessed on: 29th August 2024.
2. AstraZeneca. Clinical study report for osimertinib for the treatment of EGFR mutation-positive non-small cell lung cancer. A Phase III, Randomised, Double-Blind, Placebo-Controlled, Multicentre, International Study of Osimertinib as Maintenance Therapy in Patients with Locally Advanced, Unresectable EGFR Mutation-Positive Non-Small Cell Lung Cancer Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-Based Chemoradiation Therapy (LAURA). Data on file. 2024.

Appendix

Figure 1: Overall Survival Plot for EAG Base Case

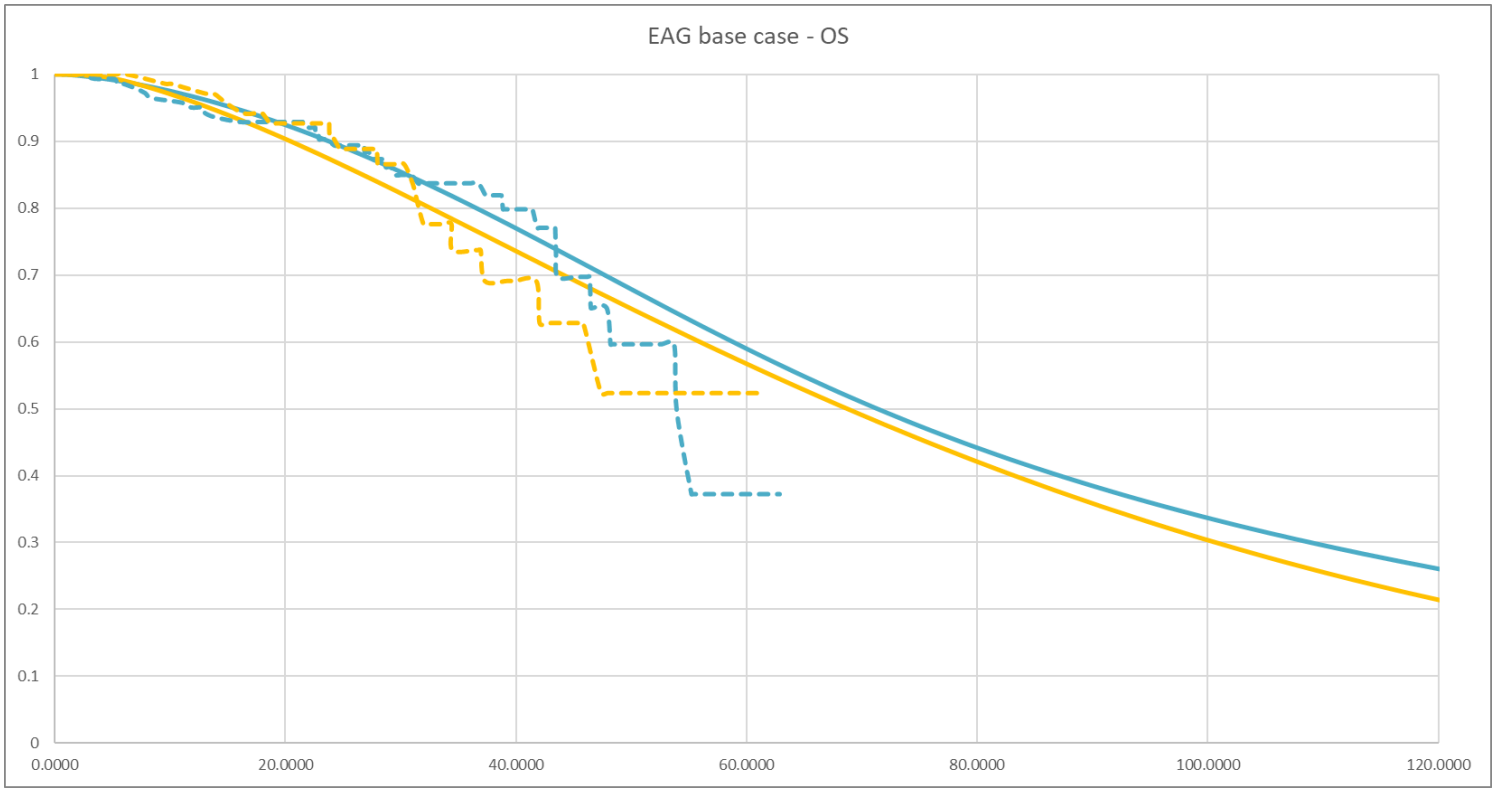
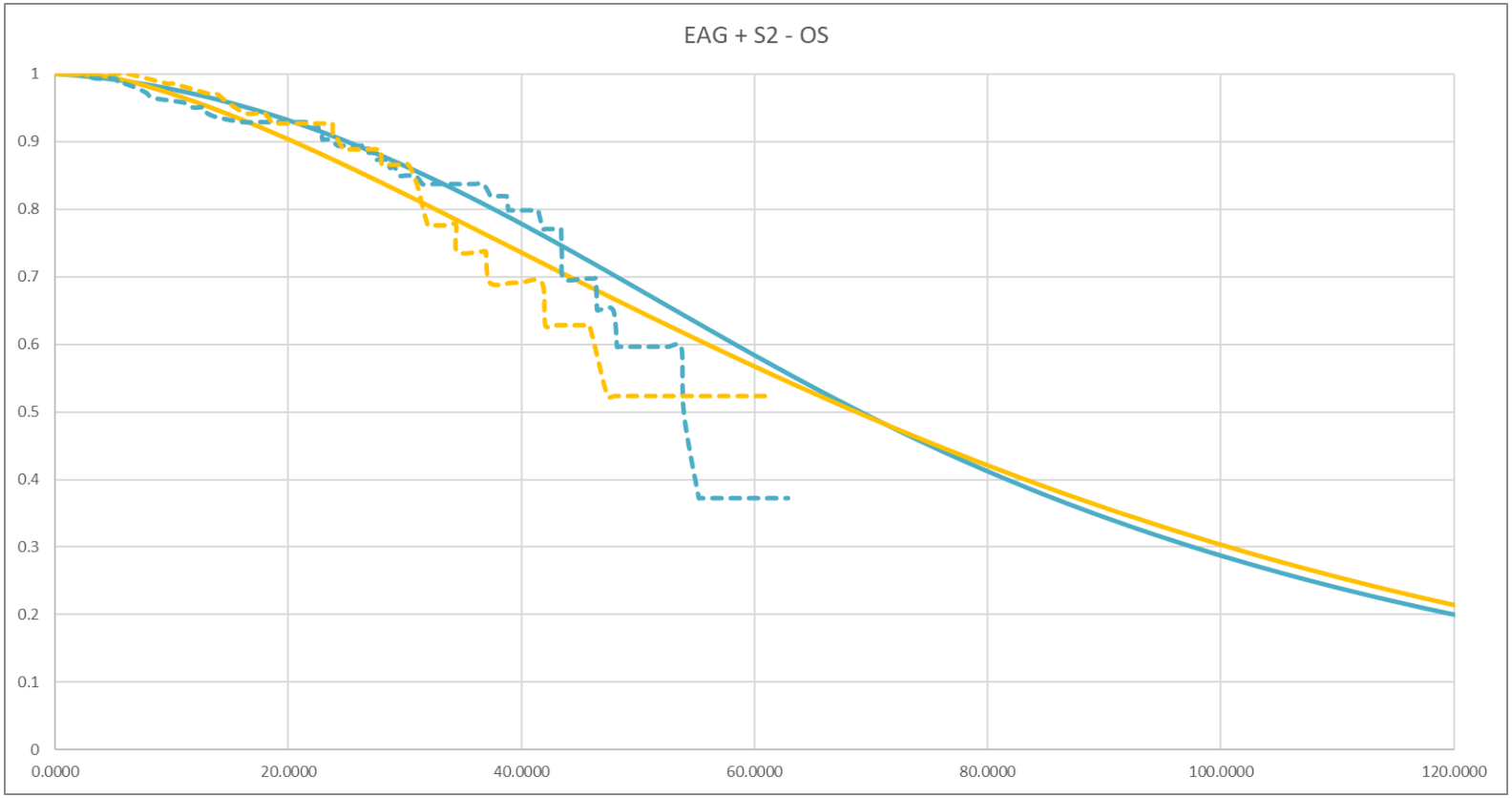


Figure 2: Overall Survival Plot for EAG Scenario C2 (EAG + S2)



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation [ID6223]

Clarification questions post-FAC

17 April 2025

Section A: Clarification on LAURA trial OS data

A1. In response to clarification question B5, the company provided the mean osimertinib treatment duration (5 January 2024 DCO) for LAURA trial placebo arm patients who had received osimertinib as a subsequent treatment. The mean LAURA trial value was lower than the value used in the company model; however, the company considered that the LAURA trial data were too immature to use in the economic model.

Please provide the mean osimertinib treatment duration (29 November 2024 DCO dataset) for LAURA trial placebo arm patients who received osimertinib as a subsequent treatment. Please provide the number of LAURA trial placebo arm patients who were still being treated with osimertinib as a subsequent treatment (29 November 2024 DCO).

The additional data cut-off (DCO) focused on an update to overall survival (OS) including an updated hazard ratio and Kaplan-Meier curves. These data were provided to help validate the model-predicted OS and reduce uncertainty in this appraisal. The 29 November 2024 DCO did not include analysis of treatment duration therefore, we are unable to provide the information requested.

A2. Results from analyses of LAURA trial data (5 January 2024 DCO) showed that the proportion of patients who discontinued osimertinib and received osimertinib as a subsequent treatment was 23.8% (15/63; CS, Table 11). However, results from analyses of November 2024 DCO LAURA trial data showed that this proportion had increased to 29.7% (22/74).[1] Using data from the November 2024 DCO for patients in the LAURA trial osimertinib arm who received osimertinib as a subsequent treatment, please provide:

- mean osimertinib treatment duration

[1] https://www.oncologynewscentral.com/nsclc/data-back-osimertinib-after-chemoradiotherapy-as-new-standard-of-care-for-some-nsclc

- the number of patients by reason for treatment discontinuation (disease progression, unacceptable toxicity etc.)

As stated above in response to question A1, treatment duration was not analysed as part of the November 2024 DCO. In addition to OS, only the number of patients who discontinued study treatment and the type of subsequent treatment those patients received were analysed. No additional data were extracted for analysis therefore, we are unable to provide the data requested. Further, NHSE blueteq criteria would preclude the usage of subsequent osimertinib after receiving the LAURA regimen therefore data on treatment duration and discontinuations are not relevant for UK clinical practice.

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation**
Topic ID: **6223**
Managed Access Lead: **Milena Wobbe**
Date of assessment(s):

Is Managed Access appropriate - Overall rating	Comments / Rationale
Yes	The managed access team believe that a period of managed access would enable a robust submission upon exiting the CDF with an economic analysis that includes mature OS data as well as more robust data on post progression survival, enabling an extrapolation with reduced uncertainty. Most uncertainties have a significant impact on the cost effectiveness results. Further data collection would enable some reduction in uncertainties.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	This is an anti-cancer medicine and therefore eligible for funding through the CDF.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Yes	Some uncertainties could be resolved through further data collection while some uncertainties require committee judgement to be resolved.
Can data collection be completed without undue burden on patients or the NHS system	Yes	There is an ongoing clinical trial (LAURA) and the SACT data set is available for data collection.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	No	

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update		
pre-committee data collection working group		
pre-committee patient involvement meeting		

Key questions for committee if Managed Access is considered	
1	
2	

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	This is an anti-cancer medicine and is therefore eligible for funding through the CDF

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
High	There are significant uncertainties around the LAURA trial data which informs the model. Some of these uncertainties are unresolvable. However, the managed access team believe that a period of managed access would address some key uncertainties through further data collection. A key uncertainty is the effect of OS on the cost effectiveness, as the data has not been incorporated into the economic model directly due to its immaturity. It is understood that whilst a further data cut can be shared during this appraisal, as period of time in the CDF would enable the OS data to reach maturity and be incorporated fully within the economic model upon exit. The highest impact on ICER related to post-progression outcomes which are also not mature on the whole and further data collection from the LAURA trial could allow committee to make judgement calls with less uncertainty.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes

EAG1	Limitations of the osimertinib clinical effectiveness evidence	Clinical advice to the EAG is that, overall, the baseline characteristics of the LAURA trial patients are representative of NHS patients with EGFRm-positive locally advanced unresectable NSCLC that has not progressed during or following CRT. However, compared to NHS patients: •a higher proportion of LAURA trial patients were Asian •no LAURA trial patients were black. Clinical advice to the EAG is that the clinical effectiveness of osimertinib is unlikely to be affected by ethnicity. The Asian subgroup PFS HR was 0.20 (95% CI: 0.13 to 0.29) whereas the non-Asian subgroup PFS HR was 0.48 (95% CI: 0.20 to 1.19); however, the non-Asian subgroup only included a very small number of patients and the number of events was low (non-Asian osimertinib patients: n=14/27; non-Asian placebo patients: n=8/11) and therefore it is difficult to draw conclusions about the PFS treatment effect for patients in this subgroup.	None	Unquantified	Seek further clinical opinion to determine whether LAURA trial results can be generalised to NHS patients.	Further evidence submission ahead of ACM	No further data collection possible / proposed	SACT does not collect PFS and therefore cannot offer insight into the appropriateness of the comparison of the trial data to NHS clinical practice. Whilst a period of further data collection could not resolve this uncertainty, committee judgement could.
EAG2	Representativeness of LAURA trial placebo arm results	Clinical advice to the company was that LAURA trial placebo arm results were “poor” compared to results expected in NHS clinical practice; clinical advice to the EAG is that outcomes for NHS patients with EGFRm-positive locally advanced unresectable NSCLC following CRT are uncertain. The company identified six studies that reported PFS for patients with EGFRm-positive locally advanced unresectable NSCLC following CRT. The LAURA trial placebo arm median PFS was lower than the median PFS reported in the identified studies.	None	Unquantified	Seek further clinical opinion of whether LAURA trial placebo arm results can be generalised to NHS patients treated with BSC.	Further evidence submission ahead of ACM	No further data collection possible / proposed	A period of managed access cannot address comparator uncertainties. Whilst a period of further data collection could not resolve this uncertainty, committee judgement could

EAG3	Unclear long-term impact of treatment with osimertinib on OS	Compared with placebo, maintenance treatment with osimertinib numerically improved OS. The EAG considers that it is currently difficult to draw conclusion about the osimertinib OS treatment effect as data are immature (at the time of the 5 January 2024 DCO, the LAURA trial OS data were only 19.9% mature) and 50/62 (80.6%) LAURA trial placebo patients received osimertinib after first progression.	None	Unquantified	The final OS analysis will be conducted when the data are approximately 60% mature. Seek clinical opinion on the long-term impact of treatment with osimertinib on OS.	LAURA clinical trial	High	Whilst the OS data has not been directly incorporated into the model, further data is being collected through the clinical trial programme. NICE is expecting further data concerning a data cut with approx. 30% maturity in due course. A period of managed access would enable the incorporation of mature OS data into the economic model upon exit.
EAG4	Post-progression survival for patients initially treated with BSC	At the time of the 5 January 2024 DCO, LAURA trial placebo arm PPS data were only 21% mature and 50/62 (80.6%) of patients had received osimertinib as their first subsequent treatment. In the company model, mean survival in the PD health state for patients initially treated with BSC who receive osimertinib as their first subsequent treatment is substantially lower than the expected survival of patients treated with osimertinib as a first-line treatment in the metastatic setting (TA654).	Use the Weibull distribution to generate PPS estimates for patients initially treated with BSC.	High	Seek clinical opinion on the expected PPS of patients initially treated with BSC.	LAURA clinical trial	Medium	Further OS data cuts are expected beyond the timeframe of the NICE appraisal. NICE is expecting a more recent data cut with 30% OS data maturity during this appraisal, which will also address some PPS data. Managed access data collection is limited to up to five years, which means that extrapolation to a longer timeframe is still required and some committee judgement will be required. This uncertainty has the highest impact on the ICER.
EAG5	Osimertinib time to treatment discontinuation	The company generated osimertinib TTD estimates using LAURA trial K-M data up to 36 months and an exponential distribution thereafter. The sustained separation of the PFS and TTD curves after 36 months is not supported by LAURA trial PFS and TTD K-M data. The company assumed that no patients would remain on treatment with osimertinib after 10 years; a treatment stopping rule is not included in the osimertinib expected licence or the LAURA trial protocol.	i) Use the same distribution to generate osimertinib PFS and TTD estimates from the start of the model time horizon. ii) Remove the 10-year osimertinib treatment stopping rule.	High	None	LAURA clinical trial / committee judgement required	Low	Whilst SACT cannot collect PFS data, TTD data would be reasonable to collect. A period of further data collection could enable further data collection for TTD and PFS in the clinical trial and TTD in the NHS. Committee may choose to use their judgement to resolve this uncertainty, as it is a modelling choice.

EAG6	Proportion of patients receiving subsequent treatment	In the company model, i) the proportion of patients who received at least one subsequent treatment and ii) the proportion who received osimertinib as a first subsequent treatment were based on the average of clinical expert estimates. These estimates are lower than observed in the LAURA trial.	Use estimates informed by LAURA trial data so that modelled costs and post-progression survival are aligned.	Medium	Proportion of people receiving subsequent treatment and the proportion of people who received osimertinib as a first subsequent treatment	SACT	High	SACT data could help address this uncertainty within NHS clinical practice.
EAG7	Company model health state utility values	The company PF utility value exceeds the general population utility value (age- and sex- matched to LAURA trial baseline characteristics). The company PD utility value does not reflect the decline in HRQoL that occurs as disease progresses.	i) Set the PF utility value to the age- and sex-matched general population utility value. ii) Set the PD utility value to the average of the TA654 PFS and PD utility values.	Medium	None	Committee judgement required	No further data collection possible / proposed	Whilst further data collection could not resolve this uncertainty, committee judgement could.
EAG8	Post-progression survival for patients initially treated with osimertinib	LAURA trial osimertinib arm PPS follow-up was short and few patients were at risk of post-progression death. PPS for patients initially treated with osimertinib may be underestimated.	Use the exponential distribution to generate PPS estimates for patients treated with osimertinib	Medium	Seek clinical opinion as to the expected PPS of patients initially treated with osimertinib	LAURA clinical trial	Medium	Further OS data cuts are expected beyond the timeframe of the NICE appraisal. NICE is expecting a more recent data cut with 30% OS data maturity during this appraisal, which will also address some PPS data. Managed access data collection is limited to up to five years, which means that extrapolation to a longer timeframe is still required and some committee judgement will be required.
EAG9	Time to progression and progression-free survival for patients treated with osimertinib	The company selected the Weibull distribution to generate TTP and PFS estimates for patients treated with osimertinib. It is uncertain whether the hazard of progression implied by the Weibull distribution represents the change in hazard observed in the LAURA trial osimertinib arm and produces clinically plausible long-term PFS estimates.	Use the exponential distribution to generate TTP and PFS estimates for patients treated with osimertinib	High	Seek clinical opinion as to which distribution produces the most clinically plausible hazard of progression and long-term PFS estimates.	LAURA clinical trial / committee judgement required	Low	Trial data is available up until 75 months, with data having reached maturity. Further data collection trough the LAURA trial might enable better curve fitting. However, this data would be unlikely to produce more accurate or trusted curves beyond the observed data.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
High	The clinical trial programme is still ongoing, although primary completion happened in January 2024.

LAURA Clinical trial data	
Anticipated completion date	Jun-26
Link to clinicaltrial.gov	https://clinicaltrials.gov/study/NCT03521154
Start date	Jul-18
Data cut presented to committee	Jan-24
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/33558193/
Description of trial	A Phase III, Randomized, Double-blind, Placebo-controlled, Multicentre, International Study of Osimertinib as Maintenance Therapy in Patients With Locally Advanced, Unresectable EGFR Mutation-positive Non-Small Cell Lung Cancer (Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-based Chemoradiation Therapy (LAURA), n=216. Primary outcome measure: PFS, secondary outcomes measures (not complete list): Time to CNS PFS, OS, …

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
High	SACT dataset would enable further data collection

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	NHS England's SACT dataset is an established mandatory dataset
Prior experience with managed access	High	NHS England's SACT Team have extensive experience with managed access in the Cancer Drugs Fund
Relevance of existing data items	High	
If required, ease that new data items can be created / modified	Not applicable	No additional data items to be included
How quickly could the data collection be implemented	Normal timelines	SACT is an existing mandatory dataset. No additional time is required to implement data collection in clinical practice
Data quality		
Population coverage	High	SACT is an existing mandatory dataset that will capture the entire population treated with the medicine in clinical practice
Data completeness	High	NHS England's SACT Team have established processes in place to ensure high data completeness. Cohort of interest is identified by Blueteq records and NHS Digital follow-up with trusts where data is missing
Data accuracy	High	SACT is an established mandatory dataset and there is a good understanding of using SACT in clinical practice. NHS England's SACT Team have a dedicated help desk and follow-up with trusts where data submitted is ambiguous or lacks face validity
Data timeliness	High	Trusts submit records to the SACT dataset monthly
Quality assurance processes	Yes	Dedicated SACT data liaison officers and SACT helpdesk. Established process to ensure data quality available at: http://www.chemodataset.nhs.uk
Data availability lag	Low	Four months are required from data collection to allow for data to be uploaded to SACT, follow-up of missing data, and analysis and production of NHS England's SACT Team's report
Data sharing / linkage		
New data sharing arrangements required?	No	Data sharing agreements between NHSE, SACT, blueteq and Personal Demographics Service (vital status) have been previously established
New data linkages required?	No	Data linkage has been previously established to allow NHSD to link blueteq applications to SACT activity to identify the cohort of interest.
If yes, has the governance of data sharing been established	Not applicable	
Analyses		
How easily could collected data be incorporated into an economic model	High	

Existing methodology to analyse data	Yes	Established methodology available here: http://www.chemodataset.nhs.uk
If no, is there a clear process to develop the statistical analysis plan	Not applicable	
Existing analytical capacity	High	Established analytical capacity
Governance		
Lawful basis for data collection	Yes	6(1)e of the United Kingdom General Data Protection Regulations (UK GDPR). Statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021
Privacy notice & data subject rights	Not applicable	Mandated dataset as part of the Health and Social Care Information Standards
Territory of processing	Yes	UK
Data protection registration	Yes	
Security assurance	Yes	
Existing relevant ethics/research approvals	Not applicable	
Patient consent	Yes	
Funding		
Existing funding	Yes	Established partnership between NHS England's CDF team and SACT team (part of NDRS)
Additional funding required for MA	No	
If yes, has additional funding been agreed in principle	Not applicable	
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?	No	Established mandatory dataset. No additional data items created
Are any of the clinical assessments not validated for use or accepted clinical practice	No	See above
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation	No	Data collection mandated by a Data Collection Agreement would be used for the purpose of the NICE guidance update
Additional considerations for managed access		

Are the clinical assessments and data collection comparable to current clinical practice data collection?	Yes	Established mandatory dataset. No additional data items created
Burden		
Additional patient burden	No	Existing mandated data set. No additional burden of data collection within managed access
Additional clinical burden	No	Existing mandated data set. No additional burden of data collection within managed access
Other additional burden	No	

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
No	No substantive issues identified.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	
	Expected overall additional system burden from data collection?	Low	
	Do stakeholders consider any additional burden to be acceptable	Yes	
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	No	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	
	Is there a clear plan to monitor patient safety within a MA?	Yes	
	Are additional patient safety monitoring processes required	No	

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	No	
	Will implementation subject the NHS to irrecoverable costs?	No	
	Is there an existing service specification which will cover the new treatment?	Yes	

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	

Patient eligibility	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	