Single Technology Appraisal

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

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:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response
   b. Follow-on clarification response

3. **Patient group, professional group and NHS organisation submissions** from:
   a. EGFR Positive UK

4. **Expert personal perspectives** from:
   a. Dr Elizabeth Toy – clinical expert, nominated by AstraZeneca
   b. Professor Eric Lim – clinical expert, nominated by AstraZeneca
   c. Gini Harrison – patient expert, nominated by EGFR Positive UK

5. **External Assessment Report** prepared by School of Health and Related Research, University of Sheffield
   a. External assessment report
   b. Additional figures and graphs pre ACM1

6. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small cell lung cancer after complete tumour resection

Document B

Company evidence submission

January 2024

File name	Version	Contains confidential information	Date
ID5120_Osimertinib_Document B_[CIC redacted]_10Jan24	**1**	**Yes**	**10.01.24**

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Abbreviations

AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ASCO	The American Society of Clinical Oncology
BIC	Bayesian information criterion
BSA	Body surface area
CAA	Commercial access agreement
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DF	Disease free
DFS	Disease-free survival
DM	Distant metastasis
DSA	Deterministic sensitivity analysis
DSU	Decision support unit
EGFR	Epidermal growth-factor receptor
EGFRm	Epidermal growth-factor receptor mutation
EGFR-TK	Epidermal growth-factor receptor tyrosine kinase
EGFR-TKI	Epidermal growth-factor receptor tyrosine kinase inhibitor
EMA	European Medicines Agency
ERG	Evidence review group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EOT	End of treatment
FDA	United States Food & Drug Administration
GLS	Generalised least squares
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
IDMC	Independent Data Monitoring Committee
ILD	Interstitial lung disease
KM	Kaplan-Meier
LRR	Locoregional recurrence
LYG	Life-years gained
MCM	Mixture cure model
MCS	Mental component summary (SF-36)
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
MSE	Mean squared error
MSM	Multi-state model
N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OCE	Oncology Center of Excellence
OS	Overall survival
PAS	Patient access scheme
PCS	Physical component summary (SF-36)
PDC	Pemetrexed and cisplatin
PET-CT	Positron emission tomography computed tomography
PFS	Progression-free survival
PH	Proportional hazards
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY(s)	Quality adjusted life year(s)
QoL	Quality of life
RDI	Relative dose intensity
RMME	Repeated measures mixed effect
SAE	Serious adverse event

Seer	Surveillance, Epidemiology, and End Results Program
SF-36	36-item short form health survey questionnaire
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
TP	Transition probability
TTD	Time to treatment discontinuation
WHO	World Health Organization
WTP	Willingness-to-pay

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

B.1.1 *Decision problem*

The objective of this single technology appraisal is to evaluate the clinical- and cost-effectiveness of osimertinib (with or without prior chemotherapy) as adjuvant treatment of epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) after complete tumour resection.

The submission covers the technology's full marketing authorisation for this indication; the osimertinib indication relevant to this appraisal is for the adjuvant treatment after complete tumour resection, with or without adjuvant chemotherapy, in adult patients with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

The submission presents data for the comparison of osimertinib with established clinical management, that is, active monitoring with or without prior adjuvant chemotherapy, in line with the relevant indication for osimertinib. This is reflected in the marketing authorisation wording,[1] which does not mandate whether or not patients should receive adjuvant chemotherapy prior to initiation of adjuvant osimertinib. Inclusion of adjuvant chemotherapy as a comparator is not considered appropriate at the treatment decision to administer adjuvant osimertinib. The decision to administer adjuvant chemotherapy is made separately and prior to the treatment decision to administer osimertinib. The clinical effectiveness data for this appraisal is informed by the ADAURA clinical trial which was designed to evaluate osimertinib as an add-on therapy to standard practice in the adjuvant setting (i.e., surgery plus chemotherapy, if indicated), and not to define the optimal role of adjuvant chemotherapy in resected EGFRm NSCLC patients. Adjuvant osimertinib is not intended or expected to displace adjuvant chemotherapy as it represents an additional adjuvant treatment option. Therefore, the decision problem addressed by this submission is consistent with the original scope (TA761) as there is no clear rationale for deviation in this CDF exit appraisal.[2]

Data for the following outcomes are presented in the submission, in line with the NICE decision problem for osimertinib: disease-free survival (DFS), disease recurrence sites and rates, overall survival (OS), adverse events (AEs), health-related quality of life (HRQoL) and time to treatment discontinuation (TTD). The economic analysis follows the NICE reference case and therefore ensures alignment with the NICE decision problem for osimertinib.

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
Population	People with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, after complete tumour resection (with or without adjuvant chemotherapy)	As per scope	N/A
Intervention	Osimertinib	As per scope	N/A
Comparator(s)	• Platinum-based chemotherapy • Established clinical management without osimertinib (that is, active monitoring)	Use of active monitoring as only relevant comparator	As indicated in response to the draft scope, active monitoring is the only appropriate comparator for adjuvant osimertinib. The ADAURA trial was not designed to define the optimal role of adjuvant chemotherapy in resected EGFRm NSCLC patients, and the trial was deliberately designed to evaluate osimertinib as an add-on therapy to standard practice in the adjuvant setting (i.e., surgery plus chemotherapy, if indicated).[3] Adjuvant osimertinib is not intended to displace adjuvant chemotherapy, as it provides an additional option for further adjuvant therapy after the patient/clinician decision to receive/administer adjuvant chemotherapy following complete resection. This is reflected in the marketing authorisation wording,[1] which does not mandate whether or not patients should receive adjuvant chemotherapy prior to initiation of adjuvant osimertinib. Patients in the ADAURA trial, the primary source of evidence for this appraisal, were randomised after the option to receive adjuvant chemotherapy post-resection. DFS, the primary endpoint for the ADAURA trial, was measured from the point of randomisation to the point of disease recurrence or death.[3] Outcomes for patients who received a complete resection but did not progress to eligibility for adjuvant osimertinib treatment e.g. due to early recurrence or deterioration in performance status,

			have not been captured. Therefore, it would be inappropriate to extend the cost-utility analysis to incorporate costs and consequences prior to the time of randomisation in the trial. It should also be noted that prior chemotherapy use was not a stratification factor in the ADAURA trial and subgroups according to prior adjuvant chemotherapy use were not powered for significance. As such, any analysis of outcomes by prior chemotherapy use are exploratory in nature and not appropriate for incorporation into a cost-utility analysis or for payer decision-making. The Company acknowledges the communication regarding comparator selection provided by NICE on 25th October 2023, which suggests some patients who would previously have chosen to receive adjuvant chemotherapy may now decline adjuvant chemotherapy and instead progress straight to adjuvant osimertinib. As outlined above, adjuvant osimertinib availability is not intended to displace adjuvant chemotherapy use and this is reflected in the ADAURA trial design. In order to conduct the analysis outlined by NICE, a comparison of patients who receive adjuvant chemotherapy and then go on to receive active monitoring versus patients who do not receive adjuvant chemotherapy and then go on to receive adjuvant osimertinib would need to be conducted. For the reasons outlined above (randomisation point, lack of stratification, insufficient powering), there is no available evidence to conduct such an analysis and any attempt to do so, e.g. by using proxy DFS data, would be methodologically unsound and not suitable for payer decision-making. Additionally, the Company is not aware of any evidence to quantify the suggested displacement of adjuvant chemotherapy by adjuvant osimertinib. In summary, active monitoring is the only appropriate comparator for adjuvant osimertinib as it does not displace any other treatment from the current treatment

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			pathway. This is aligned with the original scope (TA761) as there is no clear rationale for deviation.[2]
Outcomes	The outcome measures to be considered include: • overall survival • disease-free survival • sites and rates of recurrence • time to treatment discontinuation • adverse effects of treatment • health-related quality of life.	As per scope	N/A
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that 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 Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The use of osimertinib is conditional on the presence of an EGFR mutation. The economic modelling should include the costs associated with diagnostic testing	The economic base case is based on the NICE reference case. A PAS price is applicable for all osimertinib indications, including the ADAURA indication, in line with the commercial access arrangement formed as part of TA654 and TA653.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	for EGFR in people with resectable, early-stage NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • NSCLC stage (IB versus II-IIIA) may be considered.	Whilst pre-specified subgroup data from ADAURA are presented in this submission (Section B.2.6.1) the cost-effectiveness analysis is based on the full population.	Pre-specified subgroups were included in the pivotal trial (ADAURA) and the relevant efficacy data are presented in this submission (Section B.2.6.1). These subgroups, which were based on demographics, cancer staging, EGFR mutation, and adjuvant chemotherapy, were not powered to detect significant effects. 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.
Special considerations including issues related to equity or equality	N/A	N/A	N/A

Abbreviations: CAA, commercial access agreement; CNS, central nervous system; EGFR, epidermal growth factor receptor; N/A, not applicable; NHS, National Health Service; NSCLC, non-small cell lung cancer; PAS, patient access scheme.

B.1.2 *Description of the technology being appraised*

Table 2. Technology being appraised

UK-approved name and brand name	Osimertinib (Tagrisso®)
Mechanism of action	Osimertinib is an oral, CNS-active TKI that targets EGFR exon 19 deletions or exon 21 (L858R) substitution mutations of the EGFR-TK.
Marketing authorisation/CE mark status	Osimertinib is recognised as an innovative therapy in the adjuvant setting and therefore the ADAURA indication was reviewed as part of Project Orbis. Project Orbis is an FDA Oncology Centre of Excellence (OCE) initiative, with a focus on high-impact cancer drugs; providing a framework for concurrent submission and review of oncology products among international partners (including MHRA).[4] The marketing authorisation for osimertinib monotherapy as an adjuvant treatment for patients with EGFRm positive, stage IB-IIIA NSCLC, was granted by the MHRA under the Orbis project in May 2021,[5,6] and by the EMA in May 2021.[7]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Osimertinib (Tagrisso®) monotherapy is indicated for:[8] • 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.
Method of administration and dosage	Osimertinib is administered as a once-daily oral tablet. Patients can take osimertinib with or without food at the same time each day. The recommended daily dose of osimertinib is 80 mg. In ADAURA, patients received osimertinib (or placebo) for 3 years or until disease recurrence or fulfilment of a criterion for treatment discontinuation.
Additional tests or investigations	EGFR mutation status should be confirmed in tumour or plasma specimens using a validated method of testing.
List price and average cost of a course of treatment	The list price for 30 tablets is £5,770. At list price, the total cost is approximately £210,000 per patient, based on expected treatment duration from the ADAURA trial (36 months) and including administration costs.
Patient access scheme (if applicable)	A PAS price of [redacted]

Abbreviations: CNS, central nervous system; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; EGFR-TK, epidermal growth factor receptor tyrosine kinase; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, non-small cell lung cancer; PAS, patient access scheme; TKI, tyrosine kinase inhibitor.

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

- **Non-small cell lung cancer (NSCLC) is the most prevalent form of lung cancer in England and Wales accounting for 80% to 85% of all cases of lung cancer[9]**
- **Activating epidermal growth factor receptor mutations (EGFRm) are a common type of genetic mutation driving oncogenesis occurring in 8% to 16% of patients with early-stage (IB-IIIA) NSCLC[10,11]**
- **The overall survival rate for patients with early-stage NSCLC after resection has been reported as 69.5% at 5 years and 52.5% at 10 years.[12]**
- **Surgical resection for patients with stage IB-III NSCLC can be curative for some patients, but between 44% and 76% of patients experience disease recurrence or death within 5 years post-surgery,[13] with 70% of these recurrences developing as distant metastases, in particular brain metastases[14]**
- **Patients with EGFRm NSCLC have a higher likelihood of metastatic recurrence and are twice as likely to develop subsequent brain metastases than patients with wild-type EGFR[15-17]**
- **Disease recurrence, especially brain metastasis, is associated with poor survival, a high symptom burden, detrimental effects on patient HRQoL, and considerable economic burden for the UK healthcare system[17-21]**
- **Prior to osimertinib, there were no targeted therapies and no therapies specifically for the EGFRm population available through routine commissioning in the adjuvant setting in UK clinical practice:**
  - Adjuvant chemotherapy provides relatively small survival benefits and is associated with substantial toxicities; therefore, some people choose not to receive this option or are not fit enough to tolerate it following surgery.[13,14,22]
  - First generation EGFR-TKIs, when used as adjuvant therapies, have not demonstrated significant survival benefits,[23] and patients receiving these therapies have shown high incidence of brain metastases, suggesting poor disease control due to poor blood-brain barrier penetration.[24,25]
- **The high rates of disease recurrence for patients with NSCLC, the increased risk and clinical burden of CNS metastases, and the lack of targeted adjuvant treatments for patients with EGFRm fully resectable disease, highlights the large unmet need for a targeted adjuvant treatment for these patients**
- **Since adjuvant osimertinib became available through the Cancer Drugs Fund it has become established as the standard of care for patients with EGFRm, stage IB-IIIA, resected NSCLC**
- **The positioning of osimertinib in the treatment pathway addresses a substantial unmet need by significantly improving long-term outcomes,**

including survival, while maintaining HRQoL in patients with NSCLC that are eligible for curative therapy[3,26,27]

B.1.3.1 *Disease overview*

Lung cancer is the third most common cancer and the leading cause of cancer mortality in the UK.[28] Between 2017 to 2019, lung cancer accounted for 21% of all cancer deaths in the UK.[29] In England, the age-standardised survival rate at 5 years for all lung cancers is 19.7% and it is estimated that 1 in 10 patients with lung cancer in the UK survives 10 years.[28,30] Overall, in the past 50 years in the UK, there have been limited improvements in lung cancer survival.[28]

Non-small cell lung cancer (NSCLC) is the most prevalent form of lung cancer in England and Wales.[9] Annually, there are approximately 34,000 new cases of lung cancer diagnosed in the UK and about 80% to 85% of cases are NSCLC.[9,31] The survival rate for patients with early-stage NSCLC after resection has been reported as 69.5% at 5 years and 52.5% at 10 years.[12] However, reporting of long-term survival for early-stage EGFRm NSCLC is limited.

Early-stage lung cancer is often asymptomatic and when symptoms appear they can be wide-ranging or non-specific e.g., cough, chest pain, dyspnoea, weight loss, fatigue, and bone pain.[32,33]

Genetic mutations can drive oncogenesis in NSCLC and activating epidermal growth factor receptor mutations (EGFRm) are a common type of mutation occurring in approximately 30% of patients with NSCLC, with a higher prevalence in younger patients, Asian populations, females, and never smokers.[17,34-36] In patients with early-stage (IB-IIIA) NSCLC, the EGFRm rate ranges between 8% and 16%.[10,11] This is consistent with estimates of 5-15% provided by UK clinicians in a series of 1:1 interviews in November 2023 (henceforth called the '2023 interviews').[37] Approximately 50% of EGFRm are exon 19 deletions and 30% to 40% are exon 21 L858R substitutions.[35,38] The remaining (<20%) consist of various rare EGFRm e.g., exon 18 mutations, exon 20 insertions mutations, and other exon 19 and 21 mutations.[38]

Despite the curative intent of current treatment strategies (see Section B.1.3.3),[39-43] patients still experience disease recurrence and distant metastases that adversely impact survival.[13,44]

B.1.3.1.1 Differences in disease recurrence in all NSCLC and EGFRm NSCLC

Due to the lack of availability of EGFR targeted treatments for early-stage NSCLC, there is limited data on recurrence rates for EGFRm patients. Literature suggests patients with EGFRm disease have a more severe course of disease and higher likelihood of metastatic recurrence.[15,16]

Recurrence rates reported for NSCLC vary according to stage of disease, with later stage disease having higher recurrence rates (44.6%, 61.8%, and 76.3% of patients with stage IB, II, and III, respectively, developed disease recurrence or death within 5 years post-surgery).[13] Post-surgical recurrence often occurs rapidly; in a cohort of patients with

completely resected, stage II to IIIB NSCLC that developed recurrence, the median time to recurrence after resection was 13.7 months despite adjuvant chemotherapy (with or without radiation) treatment.[45] Clinician estimates obtained from the 2023 interviews for the time at which patients are considered to be at the highest risk of recurrence varied from 12 months to 3 years, and depends on factors such as stage of disease and presence of N2 disease. Overall, the timepoint for highest risk of recurrence in this population was considered to be approximately 18 months.[37]

The first recurrence is local or regional in only 30% of patients.[14] Distant metastases occur in the remaining 70% of patients, after which treatment is no longer curative and is considered life-extending only.[14] Metastases, most commonly occurring in the brain (41% of patients), lung (33%), bone (24%), and liver (13%), contribute to a large proportion of treatment failures and deaths in these patients.[14]

The pattern of disease recurrence is different in the EGFRm population. Patients with EGFRm have a higher likelihood of metastatic recurrence than patients with wild-type EGFR (of the patients that recurred, 97% with EGFRm versus 68% wild-type EGFR had metastatic recurrence; p=0.0007).[15] Moreover, patients with EGFRm are twice as likely to develop brain metastases and subsequent brain metastases compared with patients with wild-type EGFR.[16,17] This higher recurrence rate in EGFRm versus wild-type EGFR may be due to the increased presence of micro-metastases in EGFRm, which are either undetectable at diagnosis or resulting from tumour cells that have spread just before or during surgery.[15] Given younger patients are more likely to be diagnosed with EGFRm NSCLC[36] and the increased risk of metastases associated with EGFRm,[15-17] it is important to provide access to a treatment option that delays disease progression or prevents CNS metastases in this patient population.

B.1.3.1.2 Cure

Patients with early-stage NSCLC can have treatment with curative intent, the mainstay of which is surgical resection.[43] Patients who remain disease-free 5 years after treatment with curative intent have a very low risk of recurrence and are considered functionally cured. At this stage patients are no longer followed up regularly, and the risk of disease recurrence or death are similar to the general population.[46] Recurrence more than 5 years after surgery is rare; less than 3% of patients with NSCLC who undergo curative resection develop recurrence more than 5 years after surgery.[12] This is in line with feedback from clinicians in the 2023 interviews, who stated that they generally consider patients who have not experienced disease recurrence within 5 years of surgery to be cured.[37] When a late recurrence does occur, it is most prevalent in patients who smoke, leading to the development of a new primary tumour.[46] For patients with post-surgical recurrence, the potential for a cure reduces as NSCLC reaches an advanced stage;[43] patients with locoregional recurrence may still be treated with curative intent with chemoradiotherapy, but for patients who experience distant recurrence or progress to distant metastasis, there are no curative treatment options available.[14,47]

B.1.3.1.3 Mortality in patients with EGFRm NSCLC

Due to the lack of availability of EGFR targeted treatments for early-stage NSCLC, there is limited data for overall survival (OS) in patients with early stage, EGFRm NSCLC.

However, it has been shown that patients with EGFRm NSCLC that develop brain metastases have a poorer prognosis, with OS estimates of less than 18 months from metastatic diagnosis.[17,18]

In US patients with EGFRm NSCLC, the median OS was significantly shorter for patients with brain metastases compared with other metastases (12 months versus 16 months, from metastasis diagnosis; p=0.017).[18]

B.1.3.2 *Burden to patients and society*

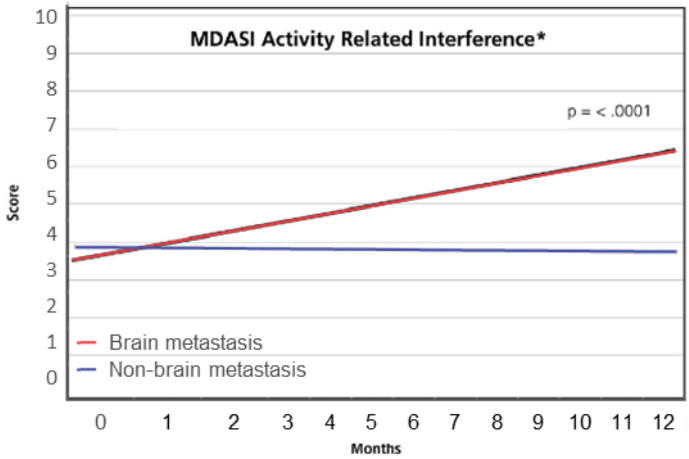
B.1.3.2.1 Quality of life burden

Compared to the general population, patients with NSCLC have poorer physical health and poorer health-related quality of life (HRQoL).[48,49]

Distant recurrence in patients with resected, early-stage NSCLC is often debilitating and leads to substantial clinical and HRQoL burden that worsens as the disease progresses and performance status declines.[50,51] In particular, brain metastases in patients with EGFRm NSCLC are associated with seizures, speech problems, focal neurological deficits, vision disorder, fatigue, nausea, headaches, problems with memory, altered mental status, and mobility issues.[18] Treatment with whole-brain radiation therapy or stereotactic radiosurgery at later stages for disease control can result in many complications, including leukoencephalopathy, neurocognitive decline, radiation-induced neurocognitive degeneration, radionecrosis, and hydrocephalus.[52,53]

This high symptom burden contributes to a clinically meaningful deterioration in HRQoL for patients with brain metastases compared with patients without brain metastases (p<0.0001; Figure 1).[19] It is this deterioration in HRQoL that underscores the importance of keeping patients in a disease-free state, thus preventing progression to distant metastatic states with CNS metastases. Additionally, patients who develop brain metastases must surrender their driving license, which one clinician at the 2023 interviews described as having a significant impact on quality of life, especially for younger patients.[37]

Figure 1. Impact of brain metastases on HRQoL in patients with NSCLC



Abbreviations: HRQoL, health-related quality of life; MDASI, M.D. Anderson Symptom Inventory.
* Higher values denote worse status of functioning
Source: Walker et al. 2018[19]

Other causes of HRQoL impairment in patients with early-stage NSCLC include experience of severe adverse events (AEs), combination treatments (e.g., with radiotherapy, chemotherapy), neurocognitive symptoms, congestive heart failure, chronic obstructive pulmonary disease, and coronary artery disease.[54]

In addition, patients with early-stage lung cancer often experience symptoms of poor mental health with 20% of patients reporting clinically significant symptoms of anxiety and approximately 10% reporting depressive symptoms.[49]

In clinical and real-world studies, patients with resected, early-stage NSCLC receiving adjuvant chemotherapy reported transient declines in physical and functional HRQoL.[55,56] Adjuvant chemotherapy also increases symptom burden with significantly more patients experiencing fatigue, anorexia, nausea, vomiting, and hair loss after initiation of adjuvant chemotherapy (up to 3 months after surgery).[55]

Caregivers of patients with NSCLC also experience detriments to their quality of life (QoL). Caring for patients with lung cancer can be physically and psychologically burdensome, especially in progressive disease as the patient's symptom burden increases and their function declines.[57] Caregiver QOL as assessed by City of Hope-QOL Scale-Family Version significantly deceased over time (6.24 to 5.84 from baseline to 24 weeks; p=0.000) with the lowest scores reported for the psychological well-being domain (5.43 to 5.12 from baseline to 24 weeks; p=0.007) (Scores from 0 to 10 with a higher score indicating better QOL).[57]

B.1.3.2.2 Economic burden

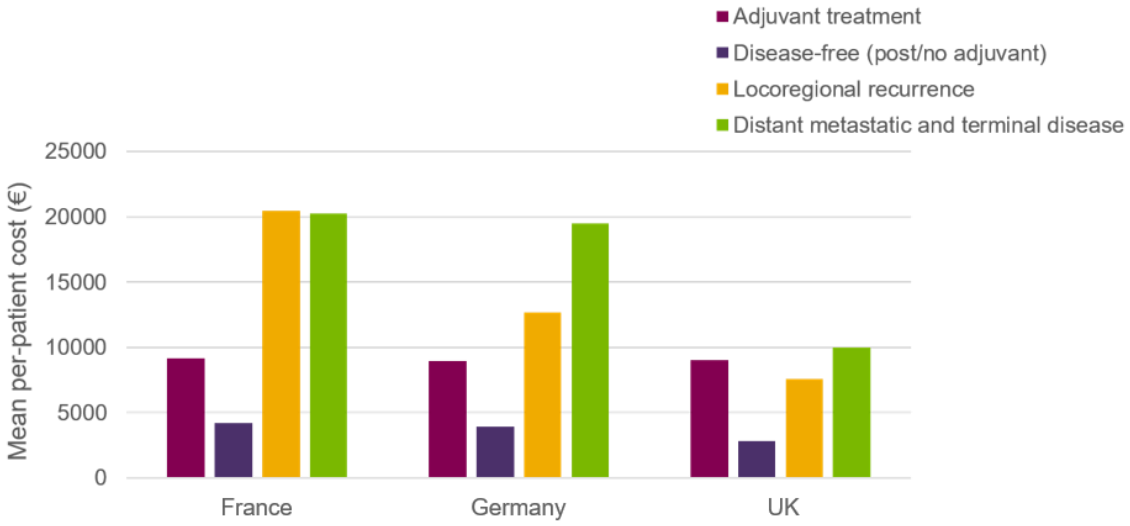
Healthcare resource utilisation and direct costs

The evidence describing the economic burden of resected NSCLC in the UK is limited. In general, the economic burden associated with the management of NSCLC within the UK healthcare system increases with disease recurrence post-resection and the location of the recurring disease.[21,44,58]

Patients with early-stage NSCLC experiencing disease recurrence post-resection have higher all-cause and NSCLC-related healthcare resource utilisation (HCRU) than non-recurrence patients.[44] This includes significantly more inpatient admissions, inpatient days, emergency department visits, and outpatient visits (all p<0.001).[44] The economic burden associated with brain metastases is primarily driven by treatment as well as healthcare costs.[20].

The LuCaBIS study[21] estimated the economic burden associated with completely resected stage IB-IIIA NSCLC and reported the direct costs were the highest for patients experiencing distant metastases, followed by those treated with adjuvant therapy (excluding targeted therapies), locoregional metastases, then disease-free state (Figure 2).[21] Note, data were collected between August 2009 and July 2012. Since then, the treatment landscape in the UK has changed but the study highlights the overall trend of increased economic burden with disease recurrence and distant metastases that is also seen in available literature examining the costs and HCRU of early-stage NSCLC.[59]

Figure 2. Direct mean costs per person associated with NSCLC for the overall follow-up period†, by country and disease phase



Notes: Study was conducted between 2009 and 2012, with a median follow-up period of 26 months, and excludes costs from targeted treatments. Cost reference year 2013/inflation-adjusted to 2013.
Abbreviation: NSCLC, non-small cell lung cancer.
† The median follow-up period for all patients was 26 months; 30 months in France, 24 months in Germany, and 25 months in the UK.
Source: adapted from Andreas et al, 2018[21]

Indirect costs

NSCLC has an impact on indirect costs. Patients of working age in the LuCaBIS study reported long-term absence from work, disability leave, and permanent disability.[21] In the UK, the mean per-patient indirect costs were estimated to be £1,159 (over 25 month period)(cost year 2013).[21] The annual cost to society, including direct, indirect, and out-of-pocket costs, of stage IB-IIIA, resected NSCLC was estimated at £267 million (cost year 2013).[21]

To quantify the impact of osimertinib for the treatment of early-stage EGFRm NSCLC on societal costs including labour productivity, transportation, informal care, sick leave benefits, and disability pensions, AstraZeneca conducted a *de novo* analysis specific to the UK setting using an economic model.[60] The model utilises the same engine as the cost-effectiveness model for efficacy (equivalent health states, transitions, and cure assumptions), and uses the time a patient spends in each health state to estimate the societal cost savings per health state. A detailed description of the methods of the osimertinib societal economic model is provided in Appendix T with a summary and the results presented below. Please note, the information contained here and in Appendix S is based on a draft manuscript in development.

[redacted]

[redacted]

[redacted]

[redacted].

B.1.3.3 *Clinical pathway of care*

The overall treatment pathway for stage IB-IIIA EGFRm NSCLC patients who have undergone complete resection, both before and with the availability of adjuvant osimertinib, is illustrated in Figure 3. This was reviewed and discussed in the 2023 interviews with UK clinicians and the below figure is considered generalisable to UK clinical practice.[37]

B.1.3.3.1 Diagnosis and staging

Diagnosis of lung cancer and staging of disease is done using a variety of tests, including chest X-rays, computerised tomography (CT), or positron-emission tomography CT (PET-CT). Lung cancer samples are commonly acquired for diagnosis using bronchoscopy, endobronchial ultrasound (EBUS), or a percutaneous procedure (guided by CT or ultrasound).[43] Genetic testing for EGFR mutations is primarily performed on biopsied tissues but can also be done on plasma samples (circulating tumour DNA) if no tissue is available.[64] EGFR mutation testing is done routinely in UK clinical practice for patients with NSCLC.[43,65] Clinicians interviewed in 2023 confirmed EGFR testing for early-stage NSCLC is part of routine practice and is conducted on biopsied tissue prior to surgery where possible.[37]

At diagnosis, staging of NSCLC is performed according to the American Joint Committee on Cancer (AJCC) staging criteria, based on primary tumour size and spread (T), lymph node involvement (N), and presence of distant metastases (M). The seventh-edition AJCC staging criteria were superseded by the eighth edition in 2017, which gives different categorisations related to tumour size, extent of nodal involvement, and metastases.[66,67] Tumour size in the eighth edition is generally smaller than that in the same stages of the seventh edition.[66] Although some patients will find their disease staging unchanged between the two editions, the introduction of the eighth AJCC edition has resulted in upstaging of some tumours compared with the seventh edition criteria,

with instances of disease previously staged as IB, IIA, IIB, and IIIA now staged as IIA, IIB, IIIA, and IIIB, respectively, and others downstaged from IIB to either IIA or IB (this list is non-exhaustive).[66]

B.1.3.3.2 Surgical and adjuvant treatment

Surgery with curative intent is the mainstay of treatment for eligible patients (patients with stage I–II disease, or with operable stage IIIA disease).[39,40,42,43] Risk of perioperative mortality and lung and cardiovascular function determine a patient's suitability for resection.[43] In England and Wales, 15% of patients with NSCLC underwent surgical resection in 2020. This rate had decreased from 20% in 2019 and was likely impacted by the COVID-19 pandemic.[62] Clinicians interviewed in 2023 estimated approximately 20% of all NSCLC patients undergo surgery and of these patients approximately 10% are EGFRm positive, although rates may vary from 5-15% across the country.[37]

Surgical resection for early-stage NSCLC can be complemented by neoadjuvant or adjuvant therapy regimens with the aim of improving long-term outcomes by reducing the risk of recurrence and increasing survival. The only neoadjuvant chemotherapy recommended in the UK is chemoradiotherapy (chemotherapy in combination with radiotherapy) for patients with operable, stage IIIA-N2 NSCLC.[43] Neo-adjuvant chemotherapy is not recommended by NICE for people with NSCLC suitable for surgery.[43]

Adjuvant chemotherapy is recommended for some patients;[43] adjuvant cisplatin-based chemotherapy is considered for patients with early stage disease, and good performance status (WHO 0 or 1).[43] However, adjuvant chemotherapy offers only modest benefits to patients; the risk of disease recurrence or death has been shown to be reduced by 16% versus no chemotherapy (HR: 0.84; $p<0.001$),[13] and the 5-year absolute survival benefit of adjuvant chemotherapy is around 5% for stage IB to stage III disease.[13,22] Not all patients are eligible to receive adjuvant chemotherapy due to the limited benefits and the significant toxicities associated with chemotherapy. Literature reports around 13%, 44%, and 50% of patients in stage IB, II, and IIIA NSCLC, respectively, receive adjuvant chemotherapy.[14] During the November 2023 interviews, clinicians reported varying levels of adjuvant chemotherapy use in UK clinical practice; estimates ranged from 25-60%.[37] Factors that influence treatment decision making for adjuvant chemotherapy include stage of disease (less likely to be given in early-stage disease), older age, presence of co-morbidities, poor performance status and oncologist/ patient choice.[37]

Post-surgery, osimertinib was recommended by NICE as an adjuvant treatment option through the Cancer Drugs Fund (CDF) in November 2021. It has since become the standard of care for patients with EGFRm NSCLC who have undergone resection, both for patients who have and who have not received adjuvant chemotherapy, as reflected in the updated ESMO guideline. [2,68] Clinicians interviewed in November 2023, since the NICE CDF recommendation, confirmed that all eligible patients are offered adjuvant osimertinib in current practice and almost all patients initiate treatment.[37]

Immuno-oncology therapies are being evaluated for the treatment of resectable NSCLC in the adjuvant and neoadjuvant settings. Nivolumab plus chemotherapy was recommended by NICE in March 2023 as a neoadjuvant treatment for patients with

resectable NSCLC.[69] However, patients with EGFRm and ALK translocation mutations were excluded from the pivotal trial evaluating nivolumab in the neoadjuvant setting.[70] As such, patients with NSCLC harbouring EGFR 19 or 21 mutations are specific exclusion criteria for neoadjuvant nivolumab treatment listed in the NHS England Blueteq Approval Criteria (September 2023).[71] Atezolizumab is another immunotherapy that is available through the CDF (i.e. is not routinely funded by NHS England) as adjuvant therapy after complete tumour resection and adjuvant chemotherapy.[72] However, the data for atezolizumab are based mainly on patients with no known EGFR mutation (EGFRm positive 11.6%, negative 52.4%, unknown 35.9%).[72]

Following surgery (with or without adjuvant chemotherapy), patients are monitored for disease recurrence over a period of 5 years. Six UK clinicians surveyed in November 2020 (henceforth called the '2020 survey') stated that, generally, patients who remain disease-free at 5 years are considered functionally cured, and are discharged from their care.[46] This is in line with a consensus statement regarding cure captured in a Delphi panel.[73] Recurrence after 5 years is rare and when it does occur, it is often due to smoking, leading to the development of a new primary tumour.[46] Since the standard of care changed with the introduction of adjuvant osimertinib, UK clinicians interviewed in 2023 stated they would consider patients functionally cured if they had not experienced disease recurrence 5 years after completing treatment with adjuvant osimertinib.[37]

B.1.3.3.3 Recurrent disease

In the event of post-surgical recurrence, the potential for a cure reduces as NSCLC reaches an advanced stage.[43] Different treatment options are available to patients with EGFRm disease based on the type of recurrence (Figure 3).

Locoregional recurrence

For EGFRm patients with locoregional recurrence, there are no targeted treatments available. Treatment options for these patients are limited to chemoradiation, and a small proportion of patients may also be offered further surgery.[46] Patients with locoregional disease may still be treated radically; around 20% of patients with locoregional recurrence in early-stage NSCLC treated with chemoradiotherapy have been shown to be progression-free after 5 years of follow-up.[47,74,75]

Disease progression to distant metastases

For patients who experience distant recurrence or progress to distant metastases, potentially curative therapies are limited.[43,76] Instead, therapies are used with the aim of extending life expectancy, but for a very small number of patients with distant metastases the care offered is palliative.[43]

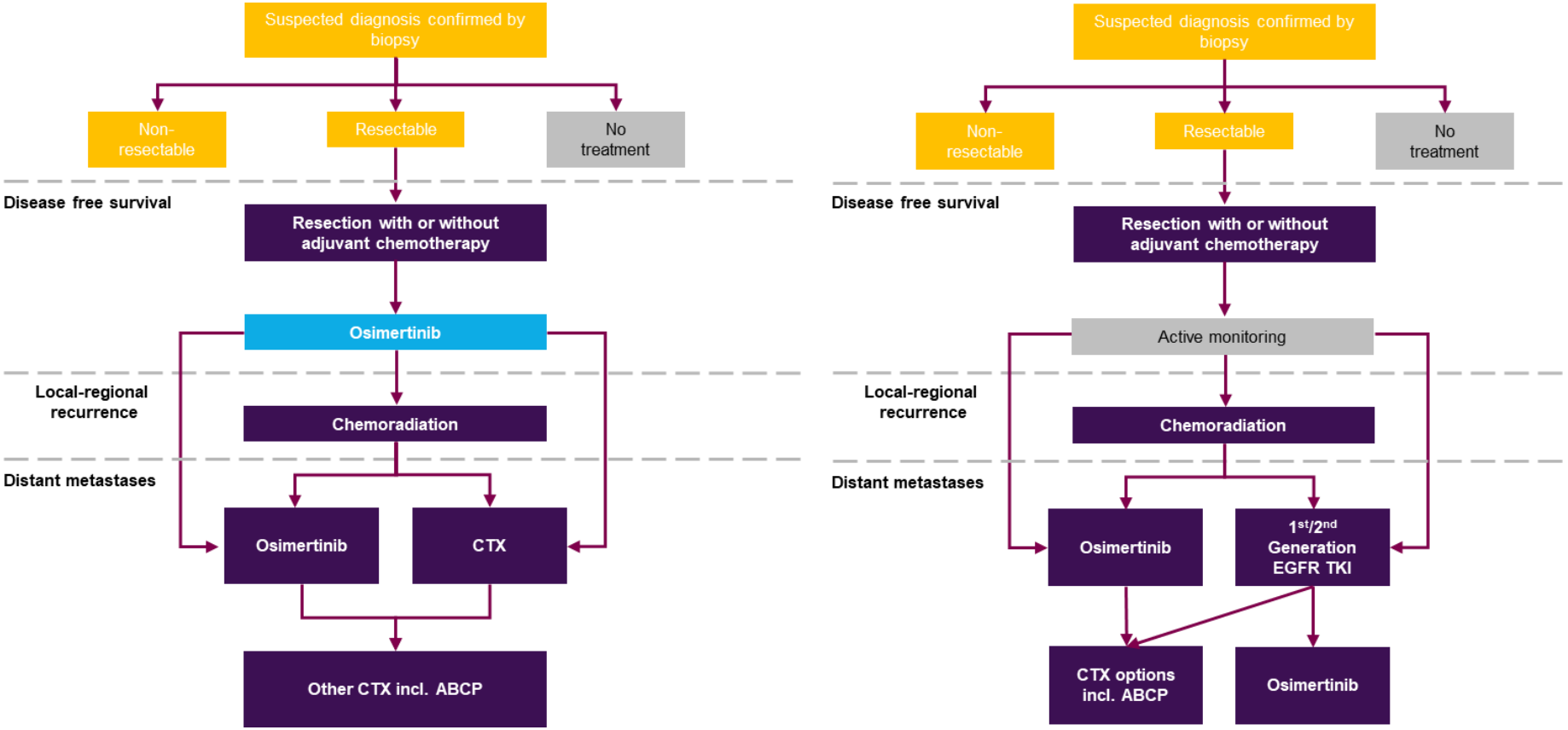
Patients who have not received adjuvant osimertinib treatment who go on to experience recurrence with locally advanced or metastatic disease can be treated with osimertinib.[77] More than 80% of patients who don't receive osimertinib in the adjuvant setting are estimated to be treated with osimertinib as a first line treatment for metastatic disease.[43,78] This was confirmed by clinicians interviewed in 2023, who stated that osimertinib is considered the standard of care for EGFRm patients in the metastatic setting and reported almost all patients would receive this options (approx. 95-100%).[37]

Patients who develop distant metastases despite adjuvant treatment with osimertinib can be re-treated with osimertinib.[2,71] UK clinical experts interviewed in November 2023 confirmed they would consider re-treating with osimertinib in the first-line metastatic setting provided patients had not experienced disease recurrence or intolerable toxicity when receiving adjuvant osimertinib.[37] Clinicians stated for patients treated with adjuvant osimertinib who have experienced disease recurrence while receiving adjuvant osimertinib, or for whom osimertinib-retreatment would not be considered for other reasons e.g. treatment-related toxicity, chemotherapy-based options would most likely be considered for first-line treatment of locally advanced or metastatic disease.[37]

Alternative first line treatments for locally advanced and metastatic disease recurrences include first- (erlotinib, gefitinib) or second-generation (afatinib, dacomitinib) EGFR-TKIs.[79-82] However, these earlier generation EGFR-TKIs are only used in a small proportion of patients in UK practice (all <10%).[78] For patients who have received adjuvant osimertinib, clinical experts advised that retreatment with EGFR-TKIs other than osimertinib is not considered as these are generally considered to be less potent and less efficacious than osimertinib and they would instead consider chemotherapy options.[37,43,81,83] Second line treatment options in the metastatic setting for patients treated with an EGFR-TKI option in the first-line setting include chemotherapy or atezolizumab plus bevacizumab in combination with carboplatin and paclitaxel (ABCP). For patients with T790 mutations treated specifically with a first- or second-generation EGFR-TKI in first-line for locally advanced or metastatic disease osimertinib is available second line. Overall, in both scenarios presented in Figure 3, given the majority of patients are expected to receive either osimertinib or chemotherapy options in first-line, second-line osimertinib use is not expected.[84,85]

Management of brain metastases includes dexamethasone to reduce the symptom burden, surgery, radiotherapy, or systemic therapies.[43,86] Bone metastases can be treated with single-fraction radiotherapy if palliation is required.[43]

Figure 3. Treatment pathway for resectable EGFRm NSCLC with and without adjuvant osimertinib



Notes: The positioning of adjuvant osimertinib in this submission is shown in blue. The treatment pathway shown here is consistent with that presented in the economic model (Section B.3). Surgery for locoregional recurrence is not shown due to the very small proportion of patients expected to be treated with this in clinical practice.
Abbreviations: ABCP, atezolizumab plus bevacizumab plus chemotherapy; CTX, chemotherapy; EGFRm, epidermal growth factor receptor mutation; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

B.1.3.3.4 Clinical guidelines

UK and European guidelines for the management of resectable NSCLC (Table 3) are generally in line with NICE guidance.[39-41,43,68] The recent European Society of Medical Oncology (ESMO) expert consensus statements on the management of EGFRm NSCLC includes the recommendation of adjuvant osimertinib for patients with resected, EGFRm, stage IB-IIIA NSCLC, in line with the marketing authorisation of osimertinib.[68] The SIGN guideline on the management of lung cancer has not been updated since 2014, before the start of the ADAURA trial.[40]

Table 3. Guidelines for surgery and adjuvant therapies in resectable disease

SIGN 137[40] **Management of lung cancer**	**ESMO[39,41,68]** **Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**
• Patients with stage I–II disease should be considered for curative surgery whenever possible • For stage IIIA NSCLC, patients with proven early N2 NSCLC may be considered for surgery as part of multimodality treatment • Patients with good performance status (PS 0–1) with completely-resected NSCLC (stage II–IIIA) should be offered platinum-based postoperative systemic anticancer therapy	**Stage IB-IIIA** • Surgery is preferred treatment • Adjuvant chemotherapy should be considered for resected stage IB and tumours >4 cm • Adjuvant chemotherapy should be offered for resected stage II • Adjuvant chemotherapy is strongly recommended for patients who undergo resection of EGFR mutant stage IB-IIIA (7th AJCC TNM edition) NSCLC with good performance status, regardless of the addition of TKI treatment. Adjuvant chemotherapy may be considered for high-risk, margin negative, stage Ib disease (7th AJCC TNM edition) with good performance status • Comorbidities, time from surgery and postoperative recovery should be considered for adjuvant therapy • Two-drug cisplatin combinations are preferred for adjuvant chemotherapy • Osimertinib is indicated for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA (7th AJCC TNM edition) NSCLC harbouring EGFR mutations • There is no solid evidence to use first- or second-generation EGFR TKI as adjuvant treatment of surgically resected EGFR-mutant NSCLC

Abbreviations: EGFRm, mutated epidermal growth factor receptor; ESMO, European Society for Medical Oncology; NSCLC, non-small cell lung cancer; SIGN, Scottish Intercollegiate Guidelines Network.
Sources: cited in table.

B.1.3.4 *Osimertinib in the treatment pathway*

B.1.3.4.1 Unmet need in the treatment pathway before adjuvant osimertinib

Surgery with curative intent is the mainstay treatment for eligible patients with early-stage NSCLC.[43] However, despite the curative intent, disease recurrence can occur

rapidly (among patients who develop recurrence, median time to recurrence has been reported as 13.7 months)[45] and disease recurrence rates are high (between 44% and 76% of patients develop disease recurrence or do not survive 5 years post-surgery).[13]

The majority of recurrences involve distant metastases at which point the disease becomes incurable.[14,20] EGFRm NSCLC is associated with a significantly higher risk of brain metastasis compared with wild-type EGFR NSCLC.[16] Disease recurrence after resection decreases HRQoL of patients and increases economic burden, in particular for those who develop brain metastases.[19-21] Furthermore, OS is significantly shorter for patients with brain metastases compared with other metastases.[18]

Adjuvant chemotherapy, which is used in some patients,[87] does reduce the risk of recurrence and improve survival, although the absolute benefits are modest.[13,22] Adjuvant chemotherapy is also associated with substantial toxicities; some people, therefore, choose not to receive it or are not fit enough to tolerate it following surgery.[14]

Prior to osimertinib, there were no targeted therapies and no therapies specifically for the EGFRm population available through routine commissioning in the adjuvant setting in UK clinical practice. First generation EGFR-TKIs, when used as adjuvant therapies, have not demonstrated significant survival benefits,[23] and have not demonstrated any evidence of reduction in the development of brain metastases, suggesting insufficient disease control due to poor blood-brain barrier penetration.[24,25]

The poor post-surgical outcomes for patients with NSCLC, the increased risk and clinical burden of CNS metastases, and the lack of targeted treatments for patients with EGFRm-positive disease highlight the large unmet need, prior to osimertinib becoming available, for a targeted adjuvant treatment for these patients improve long-term survival outcomes and potentially increase the proportion of patients who achieve cure.

B.1.3.4.2 Impact of adjuvant osimertinib on the treatment pathway

The introduction of adjuvant osimertinib has been a step change in the treatment of early-stage, resectable NSCLC, where there have been no specific therapies for patients with EGFRm NSCLC and no advancements in the adjuvant setting for NSCLC for 20 years.[2,43,88]

The positioning of osimertinib in the treatment pathway addresses a substantial unmet need among patients who undergo resection, many of whom experience disease recurrence. Osimertinib has been shown to significantly improve long-term outcomes and survival in patients with NSCLC who remain sensitive to curative therapy (i.e. resectable disease).[3,26,27] At the interim data cut-off (DCO) (January 2020) of the pivotal ADAURA trial, osimertinib demonstrated a significant DFS benefit (HR: 0.20; 99.12% CI: 0.14, 0.30) and significant improvements in CNS recurrence or death versus placebo. As such, the Independent Data Monitoring Committee (IDMC) recommended early unblinding of the ADAURA trial (2 years early).[89] Recognising osimertinib as an innovative therapy in the adjuvant setting, the Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorisation in the UK through project Orbis in May 2021,[5,6], and NICE recommended osimertinib for use as an adjuvant

treatment of patients with EGFRm, stage IB-IIIA NSCLC within the CDF as of January 2022.[2,5,6]

Since adjuvant osimertinib access was provided via the CDF recommendation, it has become established as the standard of care for patients with EGFRm, stage IB-IIIA, resected NSCLC in the UK. The final analyses of the ADAURA trial now confirm the initial DFS benefit and show that this is translated into a statistically and clinically significant survival benefit for these patients.[26,27] In addition to being the first EGFR-TKI to demonstrate significant improvements in survival outcomes in this population, it is also the first EGFR-TKI in this setting to demonstrate a significant improvement in CNS outcomes, including fewer patients with recurrence in the brain.[3,27]

Prior to the availability of adjuvant osimertinib through the CDF, active monitoring with or without adjuvant chemotherapy was the only clinical management option available for this population. Without the option to include adjuvant treatment with osimertinib, active monitoring or active monitoring and adjuvant chemotherapy, which is non-targeted and associated with toxicities and minimal survival benefits, would remain the only options available to clinicians and patients.

B.1.4 *Equality considerations*

No equality considerations have been identified in terms of patient access to osimertinib in UK clinical practice.

B.2. Clinical effectiveness

- **ADAURA is a phase 3, randomised, double-blind, placebo-controlled, multicentre study which evaluates the efficacy and safety of osimertinib (with or without prior post-operative chemotherapy) as an adjuvant therapy following complete resection in adult patients with stage IB–IIIA EGFRm NSCLC**
- **The clinical evidence demonstrates that adjuvant osimertinib with or without prior postoperative adjuvant chemotherapy results in clinically significant and unprecedented improvements in DFS and OS, a significantly lower risk of CNS recurrence or death compared with placebo, and has potential to increase the proportion of patients who achieve cure post-surgery**
- **The presented results are from the updated analyses of ADAURA; DFS DCO 11th April 2022 and OS DCO 27th January 2023, respectively. The results of the first interim analysis (DCO 17th January 2020), which were evaluated by NICE in TA761, were unblinded at a trial level two years prior to final analysis due to overwhelming efficacy**
- **In the overall population (stage IB-IIIA), treatment with osimertinib resulted in significantly longer DFS, with a 73% lower risk of disease recurrence or death vs placebo (HR: 0.27; 95% CI 0.21, 0.34)[27]**
    - In the stage II–IIIA population, treatment with osimertinib reduced the risk of disease recurrence or death by 77% vs placebo (HR: 0.23; 95% CI 0.18, 0.30)[27]
- **In the overall population, the HR for CNS DFS was 0.36 (95% CI 0.23, 0.57) indicating an 64% risk reduction in the osimertinib arm compared with placebo[27]**
- **In the overall population at 5 years, 88% of patients in the osimertinib arm and 78% in the placebo arm were alive; the overall OS HR was 0.49 (95% CI 0.34, 0.70; p<0.0001)[26,90]**
- **The OS benefit of adjuvant osimertinib was consistent across all subgroups, including with or without prior use of adjuvant chemotherapy**
- **There were minimal differences between osimertinib and placebo in SF-36 physical and mental scores at all timepoints; most patients had stable or improvements in SF-36 physical and mental component T-scores**
- **Adjuvant osimertinib with or without postoperative chemotherapy showed an acceptable safety profile, with low rates of dose modification and treatment discontinuation, and no new safety concerns were identified**
    - Interstitial lung disease (ILD) events were mild or moderate in severity and no meaningful differences in cardiac events were observed between groups

- **In addition to the ADAURA trial, data on the effectiveness of osimertinib in the adjuvant setting in UK clinical practice have been collected by NHS England in the Systemic Anticancer Therapy (SACT) dataset.**
- **The SACT data, although very immature due to a short follow up, supports the generalisability of the patient population in ADAURA.**

B.2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify publications reporting the clinical efficacy and safety of adjuvant therapies for the treatment of stage IB–IIIA NSCLC, including patients with EGFRm disease. The search strategies used in the SLR were broad to inform a number of workstreams relating to osimertinib; however, the results in the EGFRm population only are considered here, as these are of relevance to the current submission.

The SLR study question was specified using the PICOS framework (Population, Intervention, Comparator, Outcome, and Study type). Please see Appendix D for full details of the process and methods used to identify and select clinical evidence relevant to the technology being appraised.

The SLR identified a single randomised controlled trial (RCT) of osimertinib in the population of interest to this submission: ADAURA (summarised in Table 4 and reported in detail in this submission).

In addition to the ADAURA trial, data for the use of adjuvant osimertinib in clinical practice in England has been routinely collected by Public Health England within the Systemic Anti-Cancer Therapy (SACT) dataset during the period of managed access through the Cancer Drugs Fund (CDF). These data are summarised in Section B.2.6.2 and presented in detail in Appendix R.

B.2.2 *List of relevant clinical effectiveness evidence*

The systematic review of clinical evidence identified a single randomised controlled trial (RCT) of osimertinib in the population of interest to this submission (Table 4). A brief overview of ADAURA, the pivotal study of osimertinib in this indication is presented in Table 5.

Table 4. List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Is study excluded from further discussion? If yes state rationale
ADAURA	Adults aged ≥18 (or aged ≥20 in Japan and Taiwan) with WHO PS 0–1, primary non-squamous NSCLC with postsurgical pathological stage IB−IIIA and centrally-confirmed EGFR Ex19del or L858R mutation	Osimertinib	Placebo (established clinical management)	<u>Primary DFS analysis (DCO 17th January 2020):</u> Wu et al. *N Engl J Med* 2020; 383:1711-1723[3] AstraZeneca. Clinical Study Report Addendum: ADAURA. 2020[91] <u>Updated DFS analysis (DCO 11th April 2022):</u> Herbst et al. *Journal of Clinical Oncology*. 2023;41(10):1830-1840[27] Herbst et al. *Oral Presentation 2023 ASCO Annual Meeting*[90] AstraZeneca. Clinical Study Report Addendum: ADAURA. 2022[92] <u>Final OS analysis (DCO 27th January 2023):</u> Tsuboi et al. *N Engl J Med.* 2023;389:137-147[26] AstraZeneca. Clinical Study Report Addendum 2: ADAURA Final OS Analysis. 2023[93]	No

Abbreviations: DCO, data cut-off; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; N/A, not applicable; NSCLC, non-small cell lung cancer; PS, performance status; WHO, World Health Organization.

Table 5. Clinical effectiveness evidence

Study	ADAURA				
Study design	Phase 3, randomised, double-blind, placebo-controlled, multicentre study				
Population	Adults aged ≥18 (or ≥20 in Japan and Taiwan) with WHO PS 0–1, primary non-squamous NSCLC with postsurgical pathological stage IB−IIIA† and centrally-confirmed EGFR Ex19del or L858R mutation; treated with or without adjuvant chemotherapy				
Intervention(s)	Osimertinib				
Comparator(s)	Placebo (i.e., established clinical management following tumour resection)				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale if trial not used in model	N/A				
Reported outcomes specified in the decision problem	• **Overall survival** • **Disease-free survival** • Sites and rates of recurrence • **Time to treatment discontinuation** • **Adverse effects of treatment** • **Health-related quality of life**				
All other reported outcomes	• Recurrence timing • CNS recurrence (post hoc endpoint)				

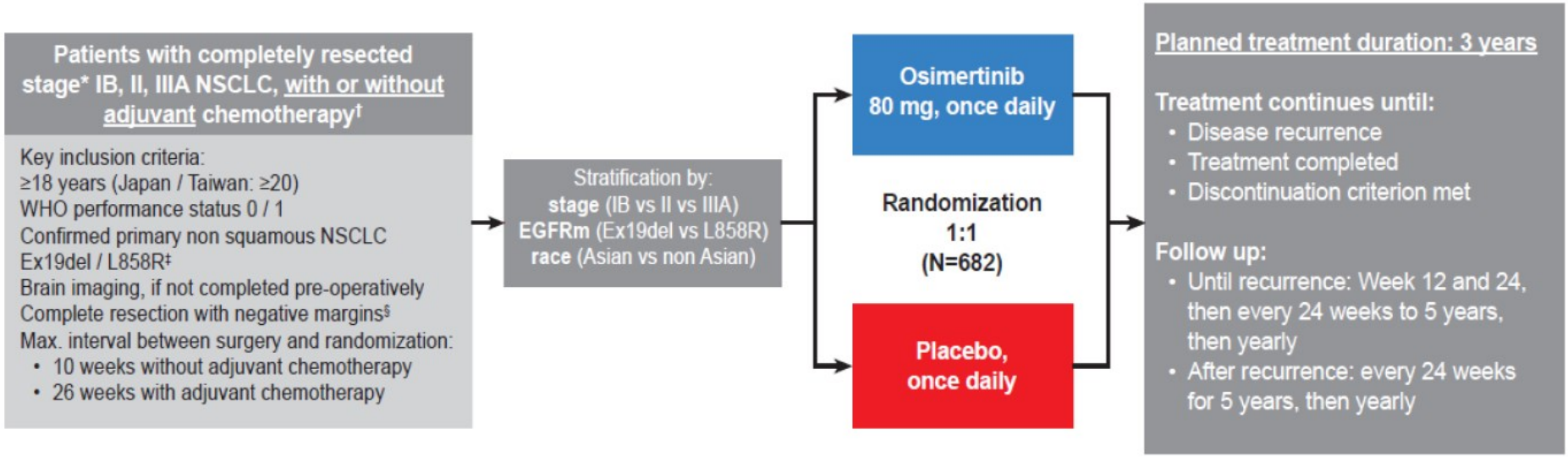
†According to the seventh edition of the AJCC Cancer Staging Manual. Outcomes in bold are included in the economic model.
Abbreviations: AJCC, American Joint Committee on Cancer; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; PS, performance status; WHO, World Health Organization.

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

B.2.3.1 *Summary of RCT methodology (ADAURA)*

ADAURA (NCT02511106) is a phase 3, randomised, double-blinded, placebo-controlled, multicentre study to examine the efficacy and safety of osimertinib as an adjuvant therapy to complete resection in adult patients with stage IB–IIIA EGFRm NSCLC. The trial design is described in Figure 4 and Table 6, with inclusion and exclusion criteria summarised in Table 7.

Figure 4. ADAURA trial design



*AJCC 7th edition. †Prior, post, or planned radiotherapy was not allowed. ‡Centrally confirmed in tissue, prior to randomisation during the screening period (maximum 4 weeks). §Patients received a CT scan after resection and within 28 days prior to treatment.
Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; EGFRm, EGFR mutation positive; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; WHO, World Health Organization.
Source: Wu et al, 2020[3]

Table 6. Summary of ADAURA methodology

Trial number (acronym)	**ADAURA**
Settings and locations	212 sites in 24 countries across Europe, Asia-Pacific, North America, and South America.
Trial design	Randomised, double-blind, placebo-controlled, multicentre, international study
Eligibility criteria for participants	Adult patients (aged ≥18, or aged ≥20 from Taiwan/Japan) with histologically confirmed primary NSCLC of predominantly non-squamous histology. Patients must have TNM-stage IB, II or IIIA disease, classified postoperatively, and have WHO performance status 0–1.
Sample size	A sample size of approximately 700 eligible patients was planned (approximately 350 per arm) to provide sufficient (80%) power to demonstrate statistical significance in the primary endpoint Number of randomised patients: • Osimertinib, n=339 • Placebo, n=343
Planned analysis	The ADAURA trial used hierarchical testing for the primary outcome. Per the statistical analysis plan, the primary endpoint was analysed first in a subset of the overall ADAURA study population, all patients with stage II–IIIA disease. If statistical significance was achieved, then testing proceeded to the overall population (stage IB-IIIA). For the purpose of this submission, the relevant population for consideration is the overall study population (stage IB-IIIA). The interim DFS analysis was planned to be conducted when approximately 247 DFS events (50% maturity) had occurred in the stage II–IIIA population, in both the osimertinib and placebo arms. At the time of the DFS interim analysis, DFS events had occurred in 156 patients (33% maturity). An exploratory analysis of DFS was to be conducted in the overall population once there had been approximately 247 DFS events in the stage II–IIIA population and approximately 70 DFS events in the stage IB subgroup. The final analysis of OS was planned to be conducted when ~94 deaths have been observed in the stage II–IIIA population (approximately 20% maturity). At the time of the final analysis 100 patients had died in the stage II–IIIA population (21% maturity) and in the overall population there were 124 events (18% maturity).
Trial drugs	**Osimertinib arm (N=339)** 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. **Placebo arm (N=343)** Matching placebo
Permitted and disallowed concomitant medication	**Permitted concomitant medications** Any medication that is clinically indicated for treatment of AEs (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 (while the patient is on study drug and/or has no disease recurrence) • Pre-medication including for the management of diarrhoea, nausea and vomiting was not allowed before the first dose of study drug
Method of randomisation and blinding	Patients were randomised 1:1 to the study arms within 10 weeks of complete surgical resection if adjuvant chemotherapy was not administered, or within 26 weeks if adjuvant chemotherapy was administered. Medication blinding was through matching placebo.
Primary outcomes (including scoring methods and timings of assessments)	DFS in the stage II-IIIA population: time to disease recurrence determined by CT or MRI, and/or pathological disease on biopsy, or death from any cause, by Investigator assessment. Baseline assessments were performed within 28 days of study drug initiation. Subsequent assessments were performed at 12 weeks, 24 weeks, and then every 24 weeks after randomisation, up to 5 years, then once yearly until disease recurrence.
Other outcomes	**Secondary endpoints** • DFS rate • HRQoL, as measured by the SF-36 (version 2) • PK plasma concentrations/ratios of osimertinib and metabolites • Adverse effects of treatment • OS and OS rate **Exploratory endpoints** • Type of recurrence • Time to next treatment†

	• PFS (by Investigator assessment)† • CNS recurrence (post hoc)
Other outcomes used in the economic model/specified in the scope	• Time to treatment discontinuation
Pre-planned subgroups	Pre-specified subgroup analyses of DFS were conducted to compare the treatment effect across disease stage, EGFR mutation type, mutation status, race, adjuvant chemotherapy, gender, age, and smoking history.

† Time to next treatment and PFS were considered to be of limited clinical significance due to data immaturity at the DCO of this analysis, and these data are therefore not presented in this submission.

Abbreviations: AE, adverse event; CT, computed tomography; DCO, data cut-off; DFS, disease-free survival; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PK, pharmacokinetic; SF-36, 36-Item Short Form Survey; WHO, World Health Organization.

Sources: Wu et al, 2020[3]; Herbst et al 2023[27,90]; clinicaltrials.gov[94]; Tsuboi et al. 2023[95]

Table 7. Key eligibility criteria for ADAURA

Inclusion criteria
• Male or female, aged at least 18 years (or aged ≥20 years in Japan/Taiwan) • Histologically confirmed diagnosis of primary NSCLC of predominantly non-squamous histology • Patients must be classified postoperatively as stage IB, II or IIIA on the basis of pathologic criteria† • Centrally-confirmed EGFR mutations known to be associated with EGFR-TKI sensitivity (either Ex19del or L858R, with or without other EGFR mutations including T790M) • Completely resected primary NSCLC with negative margins • Complete recovery from surgery and standard postoperative therapy by randomisation • WHO performance status 0–1
Exclusion criteria
• Any disallowed treatment‡ • Segmentectomies or wedge resections • Unresolved toxicities from prior therapy greater than CTCAE Grade 1¶ • Evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, or active infection including hepatitis B, hepatitis C and HIV • Any of the following cardiac criteria: mean resting QTc >470 msec; clinically important rhythm, conduction, or ECG morphology abnormalities; factors that increase the risk of QTc prolongation or risk of arrhythmic events • Active or historical ILD • Inadequate bone marrow reserve or organ function

†Staging performed according to the 7th edition TNM staging system for lung cancer.
‡ Pre/postoperative/planned radiation therapy for current lung cancer; neo-adjuvant chemotherapy; prior anticancer therapy for NSCLC other than platinum-based doublet postoperative adjuvant chemotherapy; prior treatment EGFR-TKI; major surgery within 4 weeks of the first dose; medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 week prior); treatment with other investigational drug.
¶Exceptions included alopecia and Grade 2 prior platinum-therapy-related neuropathy.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Event; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; QTc, heart-rate corrected polarisation interval; TKI, tyrosine kinase inhibitor.
Source: Wu et al, 2020[3]

B.2.3.2 *Patient disposition (ADAURA)*

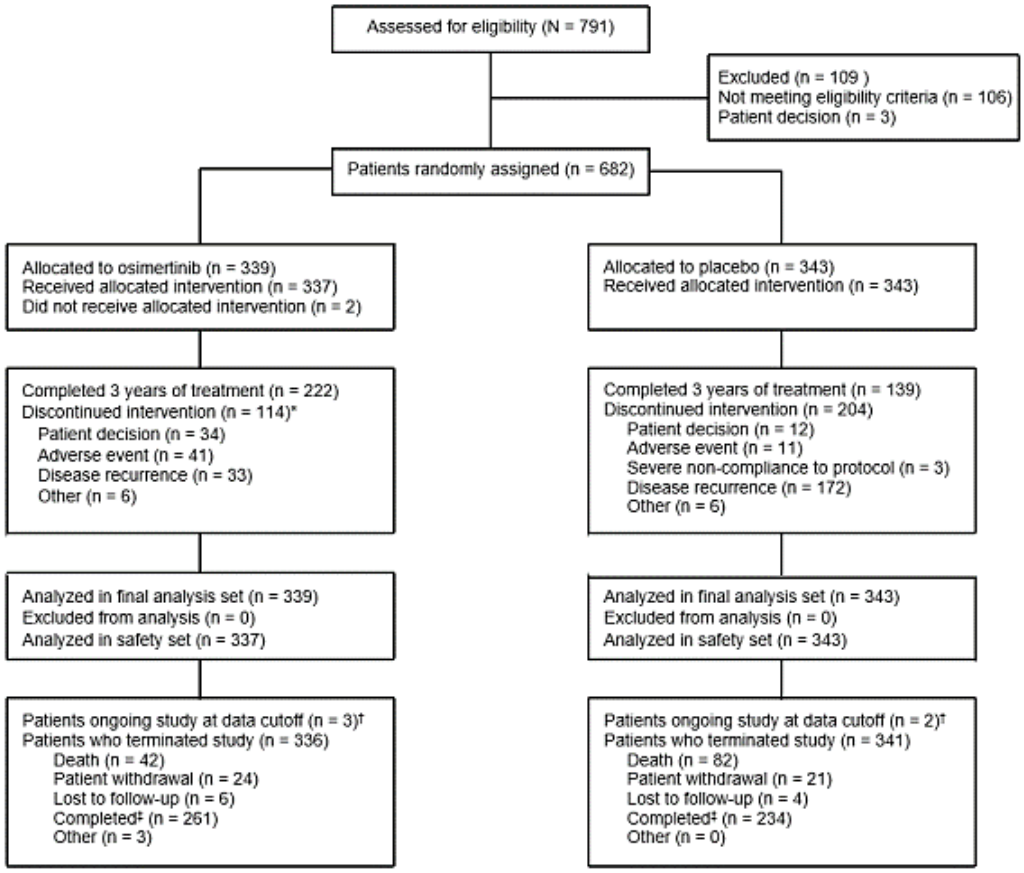
Patients were enrolled at 212 sites in 24 countries across Europe, Asia-Pacific, North America, and South America.[94]

In total, 682 patients were randomised to osimertinib (n=339) and placebo (n=343).[3] Of these, 337 and 343 patients in the osimertinib and placebo arms, respectively, received their allocated treatment (Figure 5).[3] At the time of the final DFS analysis (DCO 11 April 2022), all patients had completed or stopped study treatment.[27]

The median duration of treatment exposure was 35.8 months in the osimertinib arm and 25.1 months in the placebo arm.[27] The planned treatment duration of 3 years was completed by 66% of patients in the osimertinib arm and 41% of patients in the placebo arm.[27] In the osimertinib arm, early treatment discontinuation was most frequently due to adverse event (12.2%), patient decision (10.1%), or disease recurrence (9.8%).[26] In the placebo arm, discontinuations were most frequently due to disease recurrence (50.1%), patient decision (3.5%), or adverse event (3.2%).[26]

At the final OS DCO of 27 January 2023, the median follow-up for OS in the overall stage IB-IIIA population was 60.4 months in the osimertinib arm and 59.4 months in the placebo arm.[26]

Figure 5. Patient disposition in ADAURA



*In addition, one patient in the osimertinib group discontinued the intervention due to patient decision in 2019 but, due to partial data imputation, was documented as continuing osimertinib treatment at DCO 27 January 2023.
†No patients were ongoing in the study. Due to a data entry error, three patients in the osimertinib group and two patients in the placebo group were shown as ongoing at DCO 27 January 2023.
‡Patients who completed the study were in disease-free or overall survival follow-up when the study finished.
Source: Tsuboi et al. 2023[26]

B.2.3.3 *Patient baseline characteristics (ADAURA)*

Key baseline patient and disease characteristics are summarised in Table 8 and Table 9, respectively. Generally, the treatment arms were well matched at baseline. The majority (>60%) of patients were Asian, and approximately a third of each cohort was stage IB/II/IIIA.[3] The majority of patients had a performance status (PS) 0 at baseline, as expected, and this was similar in each arm.[3]

Table 8. Key patient demographics and baseline characteristics in ADAURA

Characteristic (FAS)	Osimertinib N=339	Placebo N=343
Median age, years (range)	64 (30–86)	62 (31–82)
Male gender, %	109 (32)	95 (28)
Race, n (%)		
White	122 (36)	122 (36)
Asian	216 (64)	218 (64)
Other	1 (<1)	2 (1)
Missing	0	1 (<1)
Smoking status, n (%)		
Never	231 (68)	257 (75)
Former	104 (31)	83 (24)
Current	4 (1)	3 (1)
Median body mass index, kg/m^2 (range)	[redacted]	[redacted]

Abbreviation: FAS, full analysis set.
Sources: ADAURA CSR[91]; Wu et al, 2020[3]

Table 9. Key disease characteristics in ADAURA

Characteristic (FAS)	Osimertinib N=339	Placebo N=343
WHO performance status, n (%)		
0	216 (64)	218 (64)
1	123 (36)	125 (36)
AJCC stage at diagnosis, n (%)		
IB	107 (32)	109 (32)
II	115 (34)	116 (34)
IIIA	117 (35)	118 (34)
EGFR mutations, n (%)		
Exon 19 deletions	185 (55)	188 (55)
L858R	153 (45)	155 (45)
Histology type, n (%)		
Adenocarcinoma		
Acinar	85 (25)	82 (24)
Papillary, malignant	43 (13)	44 (13)
Malignant	183 (54)	188 (55)
Bronchiolo-alveolar	11 (3)	13 (4)
Solid with mucous formation	4 (1)	5 (1)
Bronchial gland carcinoma (NOS)	1 (<1)	2 (1)
Carcinoma, adenosquamous, malignant	4 (1)	5 (1)
Other	8 (3)	4 (1)
Lung cancer resection type, n (%)		
Lobectomy	328 (97)	322 (94)
Sleeve resection	1 (<1)	3 (1)
Bilobectomy	7 (2)	8 (2)
Pneumonectomy	3 (1)	10 (3)
Regional lymph nodes, %		
N0	138 (41)	144 (42)
N1	97 (29)	97 (28)
N2	104 (31)	102 (30)
Adjuvant chemotherapy, n (%)		
Stage IB, received chemotherapy	[redacted]	[redacted]
Stage II, received chemotherapy	[redacted]	[redacted]
Stage IIIA, received chemotherapy	[redacted]	[redacted]

Abbreviations: AJCC, American Joint Committee on Cancer; EGFR, epidermal growth factor receptor; FAS, full analysis set; NOS, not otherwise specified; WHO, World Health Organization.
Sources: Wu et al, 2020[3]; ADAURA CSR[91]

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

B.2.4.1 *Definition of study groups*

Analysis sets in the ADAURA study included the following:

- **Full analysis set (FAS)**
  The FAS included all randomised patients and was also referred to as the 'overall population' (stage IB–IIIA patients). The FAS was used for all demographic summaries and efficacy analyses. Treatment groups were compared on the basis of randomised study treatment, regardless of the treatment actually received ('intention-to-treat'). The CSR-defined primary study population was all patients with stage II–IIIA disease, as a subset of the FAS.

- **Safety analysis set (SAS)**
  The SAS included all patients who received at least 1 dose of study treatment. Safety data were not formally analysed, but were summarised using the SAS, according to treatment actually received.

B.2.4.2 *Statistical analysis*

For the interim analysis of the primary endpoint in the CSR-defined primary study population (the stage II–IIIA population) approximately 247 DFS events were anticipated to be required in 490 patients with stage II–IIIA disease. For an assumed hazard ratio of 0.70 at a two-sided alpha level of 5%, this would provide 80% power to determine statistical significance for the comparison of osimertinib with placebo (with or without prior adjuvant chemotherapy [representing current clinical management alongside active monitoring]). The interim analysis was conducted at 156 events; to accommodate this, the Lan DeMets approach that approximates the O'Brien and Fleming spending function was used to adjust the overall 2-sided 5% type I error.[96]

To confirm a benefit conferred by osimertinib, a pre-specified hierarchical testing procedure was used. The hierarchical testing strategy was conducted as follows, with each test of statistical significance only carried out if significance was confirmed in the previous step:

1. DFS in the stage II−IIIA[a] population using the full test mass (test mass=alpha)
2. DFS in the overall population (stage IB–IIIA patients; the key population of relevance to this submission) with the test mass split between first and second analyses
3. OS[b] in the stage II–IIIA[a] population and OS[b] in the overall population with the test mass split between first and second analyses

DFS in the stage II-IIIA population and in the overall population was analysed using a log rank test stratified by stage, mutation type and race for the generation of the p-value and using the Breslow approach for handling ties. The hazard ratio (HR) and confidence intervals (CI) were obtained directly from the U and V statistics. A Kaplan-Meier (KM) plot of DFS is presented by treatment group, with the total number of events and median DFS (calculated from the KM plot, with 2-sided 95% CIs and with 2-sided 96% CIs) summarised. DFS rate data were analysed using the same model as for the primary

[a] According to staging at diagnosis.
[b] The trial was not powered for OS.

analysis of DFS. OS data were analysed using the same methodology and model as for the analysis of DFS, but with no sensitivity or subgroup analyses.

The presence of quantitative interactions was assessed by means of an overall global interaction test. This was performed by comparing the fit of a Cox proportional-hazards (PH) model including treatment, covariates for race, stage, and mutation status, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and is assessed at the 2-sided 10% significance level. If the fit of the model was not significantly improved, then it was concluded that the overall the treatment effect is consistent across the subgroups. If the global interaction test was found to be statistically significant, an attempt to determine the cause and type of interaction was made.

In order to assess possible evaluation-time bias that could occur if scans are not performed at the protocol-scheduled time points, the midpoint between the time of recurrence and the previous evaluable assessment was analysed using a log rank test stratified by stage, mutation status and race.[95]

Possible attrition bias was assessed by repeating the primary DFS analysis, except that the actual DFS times rather than the censored times of patients who recurred or died in the absence of recurrence immediately following 2 or more non-evaluable assessments, was included. For subgroup analyses, no adjustment to the significance level for testing was made since the subgroup analysis is only supportive of the primary analysis of DFS. For each subgroup level, the HR and 95% CI are calculated from a single Cox PH model that contains a term for treatment, the subgroup covariate of interest, and the treatment by subgroup interaction term. The HR is obtained for each level of the subgroup from this model.

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

A quality assessment of all trials identified in the clinical systematic review can be found in Appendix D.2.3 (separate Appendices document). The quality assessment for the ADAURA study, which is the only clinical study relevant to this submission, is presented in Table 10.

Table 10. Quality assessment results for ADAURA

	Grade (yes/ no/ unclear/ N/A)	Details
Was randomisation carried out appropriately?	Yes	Randomisation was carried out in a 1:1 fashion by IVRS/IWRS.
Was the concealment of treatment allocation adequate?	Yes	All participants were masked to treatment allocation. The IVRS/IWRS assigned the bottles of study material to be dispensed to each patient.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	All baseline characteristics were well-balanced between study arms, including PS, disease stage, EGFR mutation type, and adjuvant chemotherapy use.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Study drugs were labelled using a unique material pack code, which was linked to the randomisation code. Patients received either osimertinib or a matching placebo. The active drug and placebo tablets were identical and presented in the same packaging to ensure medication blinding. Patients and investigators remained blinded to individual treatment allocations after the interim data cut.
Were there any unexpected imbalances in drop-outs between groups?	No	Discontinuation rates were higher in the placebo arm ([redacted]) than in the osimertinib arm ([redacted]). Discontinuations in the placebo arm were primarily driven by a higher rate of disease recurrence ([redacted] and [redacted] in the placebo and osimertinib arms, respectively).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The primary and key secondary outcomes listed in the methodology section are consistent with those reported in the results section.
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	Analyses in the overall population were conducted on the FAS (i.e. ITT), comprising all patients randomised to treatment. Analyses in the stage II−IIIA population were carried out in all patients staged with II−IIIA disease (as entered into the IVRS at the time of randomisation for stratification purposes). This analysis population is a subset of the FAS. Data queries were raised for inconsistent, impossible or missing data.

Abbreviations: FAS, full analysis set; ITT, intention-to-treat; IVRS, interactive voice response system; IWRS, interactive web response system; N/A, not applicable; PS, performance status.
Sources: ADAURA CSR[92]; Wu et al, 2020[3]

B.2.6 *Clinical effectiveness results of the relevant trials*

B.2.6.1 *ADAURA Study*

The results presented in this submission are from the updated analyses of ADAURA; DFS DCO 11th April 2022 and OS DCO 27th January 2023, respectively. The results of the first interim analysis (DCO 17 January 2020) were evaluated by NICE in TA761.[2]

Per the statistical analysis plan, the primary analysis of DFS was performed on a subset of the overall ADAURA study population, patients with stage II–IIIA disease. For the current submission, the overall ADAURA population including patients with stage IB–IIIA NSCLC is the main population of relevance, as such, the results for this population are presented first, followed by the results for the stage II-IIIA population to demonstrate consistency in efficacy results.

B.2.6.1.1 Primary efficacy outcome – disease-free survival

At the final DFS analysis (DCO April 2022), data maturity for DFS was 45% for the overall population and 51% for the stage II-IIIA population.[27] This represents an increase in DFS data maturity compared to the primary analysis (DCO 17th January 2020), which had a maturity of 29% and 33% for the overall and stage II-IIIA population, respectively.[3]

Overall, the results for DFS are consistent between the primary and final analyses for both the overall and stage II-IIIA populations. In the overall population at the primary analysis (DCO January 2020), treatment with osimertinib resulted in significantly longer DFS, with an 80% lower risk of disease recurrence or death versus placebo (HR: 0.20; 99.12% CI: 0.14, 0.30; p<0.001).[3] Median DFS for the overall population was not reached with osimertinib and was 27.5 months in the placebo group. [3]

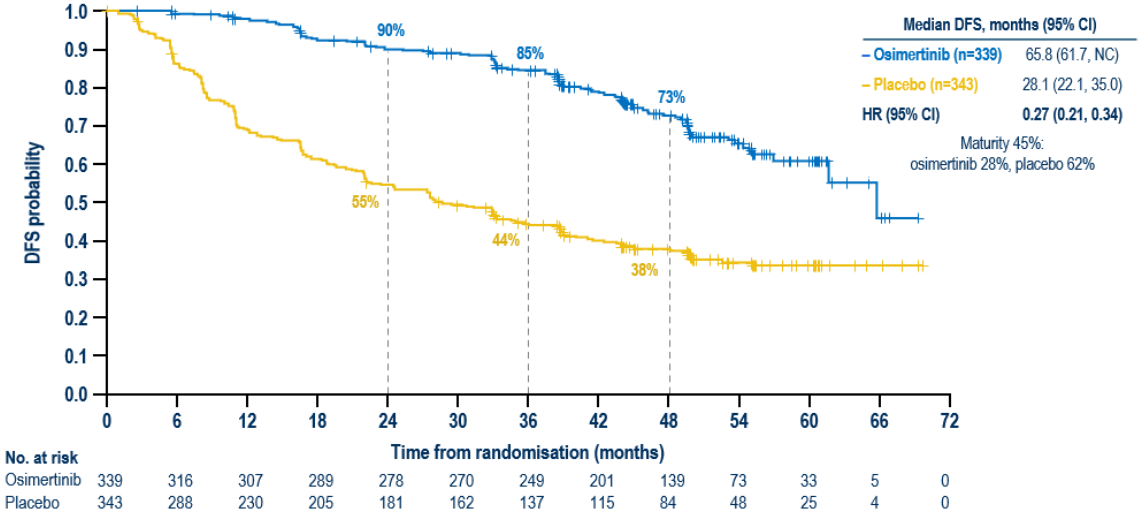
At the final DFS analysis (DCO April 2022) the DFS benefit in favour of osimertinib was sustained. In the overall population, treatment with osimertinib resulted in significantly longer DFS. Median DFS was over twice as long in the osimertinib group compared with the placebo group, at 65.8 months and 28.1 months, respectively.[27] The risk of disease recurrence or death was 73% lower with osimertinib compared with placebo (HR: 0.27; 95% CI: 0.21, 0.34) (Figure 6).[27] In line with the protocol, statistical testing for significance was not performed for the final DFS analysis, therefore p-values were not reported.[93,95] In the overall population at 48 months of follow up, the proportion of patients that were disease free and alive was nearly double for the adjuvant osimertinib group compared with placebo (72.7% and 37.8%, respectively).[27]

Early separation in the Kaplan-Meier curves was reported in the primary interim analysis,[3] and as shown below in Figure 6, separation is sustained to the last observed date in the final analysis (beyond 5 years). The curves remain separated beyond the 3-year adjuvant osimertinib treatment period, demonstrating the benefit of osimertinib treatment is clearly maintained and suggesting patients benefit from adjuvant osimertinib beyond 3 years.

The DFS curve for the placebo arm is starting to plateau at approximately 48 months follow up, which indicates that after this time point, the majority of patients are at a very low risk of disease recurrence. Interpretation of the adjuvant osimertinib DFS curve

beyond 48 months is limited due to censoring and low number of patients at risk, but is also expected to reach a plateau indicating patients are at low risk of recurrence.

Figure 6. Kaplan-Meier plot of DFS in ADAURA – final analysis for the overall population



Notes: Median follow-up for osimertinib was 44.2 months (range 0 to 69) and for placebo was 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data; HR<1 favours osimertinib.
Abbreviations: CI, confidence interval; DFS, disease-free survival; NC, not calculated.
Sources: Herbst et al. 2023[27]; Tsuboi 2022[97]

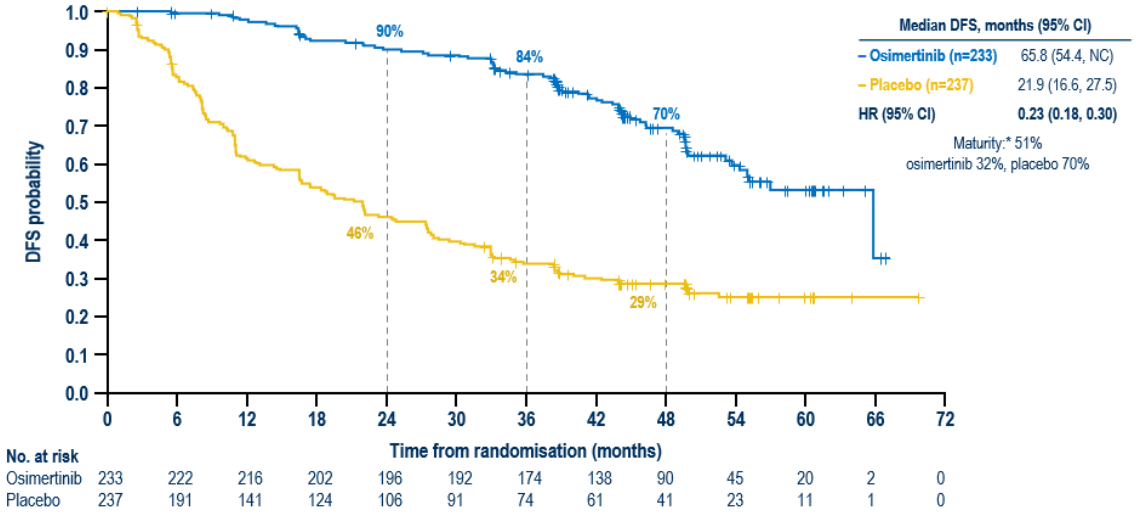
In the stage II-IIIA population at the primary analysis (DCO January 2020), treatment with osimertinib resulted in significantly longer DFS, reducing the risk of disease recurrence or death by 83% versus placebo (HR: 0.17; 99.06% CI: 0.11, 0.26; p<0.001).[3] At this analysis, the median DFS was not reached with osimertinib and was 19.6 months with placebo in the stage II-IIIA population.[3]

At the final DFS analysis (DCO April 2022), the DFS benefit in the II-IIIA population was consistent with the primary analysis (DCO January 2020) and osimertinib reduced the risk of disease recurrence or death by 77% versus placebo (HR: 0.23; 95% CI: 0.18, 0.30) (Figure 7).[27] Again, the Kaplan-Meier curves show early and sustained separation beyond 5 years in favour of osimertinib. P-values were not calculated according to the predefined protocol.[95] At the final analysis (DCO April 2022), the median DFS in the osimertinib group was three times longer that of the placebo group, at 65.8 months compared to 21.9, respectively.[27]

The DFS results for the stage II-IIIA population are consistent with the overall population at the final analysis (Figure 7).

The DFS data were reviewed by UK clinicians in 2023 interviews, who commented on the impressive nature of the treatment benefit seen with adjuvant osimertinib. The clinicians broadly agreed that the ADAURA data are expected to be generalisable to UK clinical practice, although they noted their lack of long-term experience due to the timing of the CDF recommendation.[2,37]

Figure 7. Kaplan-Meier plot of DFS in ADAURA – stage II–IIIA population



Notes: Median follow-up for osimertinib was 44.2 months (range 0 to 67) and for placebo was 19.6 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data; HR<1 favours osimertinib.
*Planned maturity for DFS analysis was 50%
Abbreviations: CI, confidence interval; DFS, disease-free survival; NC, not calculated.
Sources: Herbst et al. 2023[27]; Tsuboi 2022[97]

At enrolment, patients in ADAURA were staged according to the 7th edition of the AJCC/UICC TNM. In a *post hoc* analysis, DFS was assessed based on a re-classification of patients according to the 8th edition of the AJCC/UICC TNM staging system. The proportions of stages were similar when ADAURA patients were re-staged by AJCC/UICC 8th edition staging manual (Table 11).[97] At the final DFS analysis (DCO April 2022), HRs for each disease stage remained largely consistent between the 7th and 8th AJCC/UICC staging, favouring osimertinib.[97]

Table 11. AJCC/UICC staging at diagnosis in ADAURA according to the 7th and 8th edition

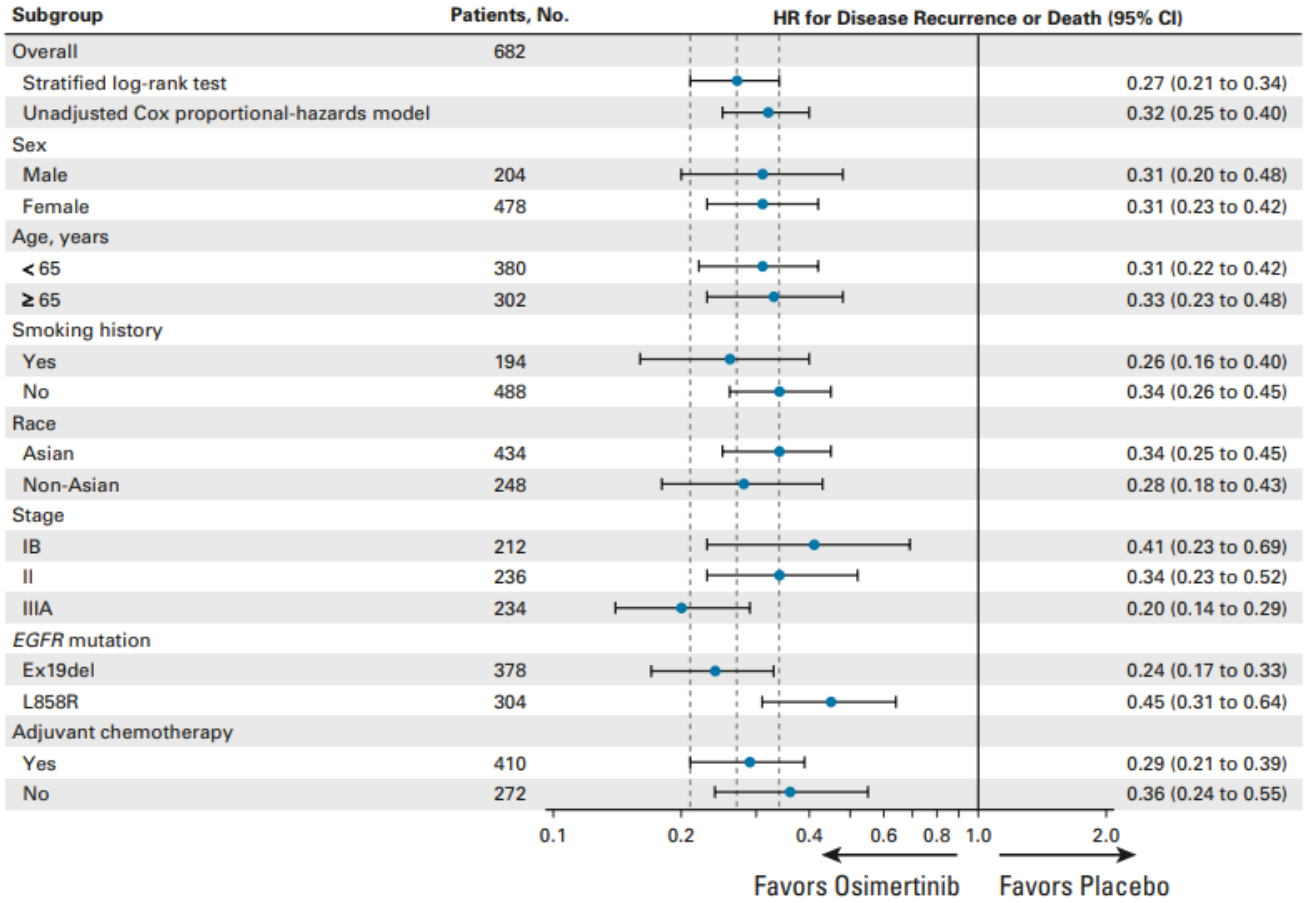
	Osimertinib	Placebo
AJCC/UICC staging at diagnosis (7th edition)		
Stage IA	0	0
Stage IB	32	31
Stage II	33	34
Stage IIIA	35	35
Stage IIIB	0	0
AJCC/UICC staging at diagnosis (8th edition)		
Stage IA	1	<1
Stage IB	30	29
Stage II	33	35
Stage IIIA	32	34
Stage IIIB	3	2

Abbreviations: AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control
Sources: Tsuboi. 2022[97]

Subgroup analysis

In the overall population at the final analysis (DCO April 2022), the DFS benefit with osimertinib was observed across all pre-defined subgroups, including for the subgroups with and without prior adjuvant chemotherapy, providing confidence in applicability of the results to patients in the UK (Figure 8).[27] UK clinicians, interviewed in November 2023, also considered the DFS benefit to be consistent across subgroups.[37] The subgroup results at the final analysis were in line with the subgroup results at the primary analysis (DCO January 2020),[3] and supported by the sensitivity analyses at the primary analysis (DCO January 2020) described in the section below.

Figure 8. Subgroup analysis of DFS in ADAURA – updated analysis in overall population



Notes: DFS subgroup analysis per investigator assessment (full analysis set; overall population); the subgroup analysis was performed using a Cox proportional hazards model including treatment, subgroup, and a treatment-by-subgroup interaction term; a HR<1 favours osimertinib.
Abbreviations: CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor.
Source: Herbst et al, 2023[27]

Sensitivity analysis

Sensitivity analyses for DFS were not repeated for the final analysis (DCO April 2022) as per the protocol.[95]

Sensitivity analyses conducted in the overall and stage II-IIIA populations for DFS based on the interim DCO (January 2020) confirmed the findings of the primary analysis in the overall and stage II-IIIA populations, respectively.

[redacted]

Disease-free survival rate

Data from the final DFS analysis (DCO April 2022) in both the overall and stage II-IIIA populations, show that the proportion of patients alive and disease free was consistently greater with osimertinib than with placebo at all assessed timepoints [36, 48, and 60 months], demonstrating a sustained DFS benefit with osimertinib during the study period (Table 12).[27]

In the overall population at 48 months, 72.7% of patients in the osimertinib group were alive and disease-free versus 37.8% in the placebo group, representing a near double increase in the DFS rate for patients treated with osimertinib.[27] Similarly in the stage II–IIIA population, over double the percentage of patients in the osimertinib group were alive and disease-free at 48 months compared with placebo, 69.5% vs 28.5% for each treatment arm, respectively.[27]

Table 12. DFS by timepoint in ADAURA

% (95% CI)	Osimertinib	Placebo
Overall population		
N	339	343
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]

% (95% CI)	Osimertinib	Placebo
Stage II–IIIA population		
N	233	237
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]

Abbreviations: CI, confidence interval.
Sources: AstraZeneca 2022[92]; Herbst et al, 2023[27]

B.2.6.1.2 Secondary efficacy outcomes

CNS DFS

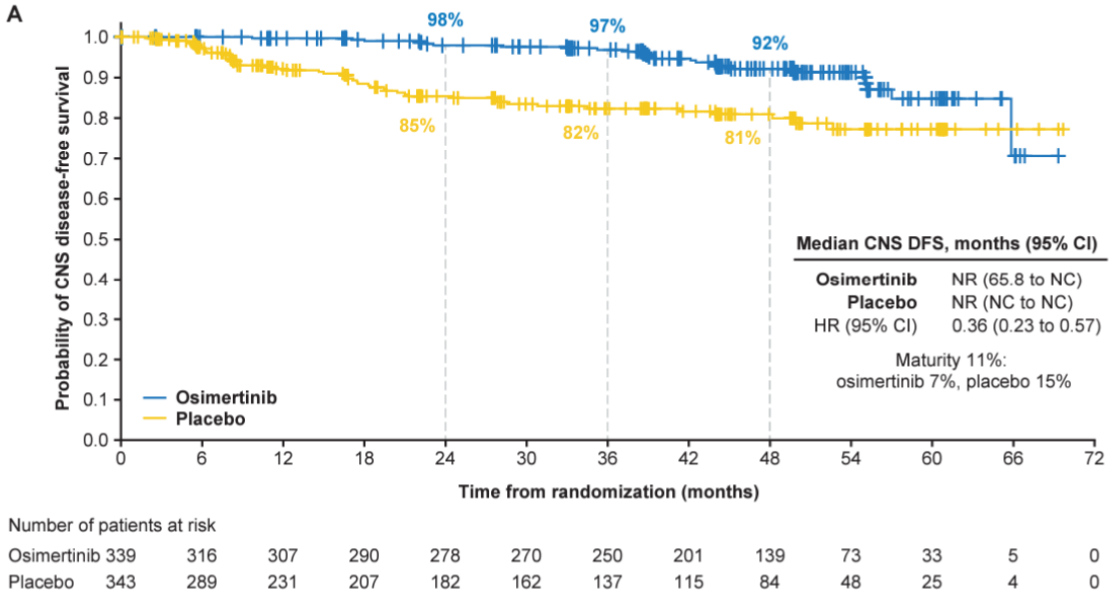
In the ADAURA final DFS analysis (DCO April 2022), a clinically meaningful and significantly lower risk of CNS recurrence or death was observed with osimertinib compared with placebo in both the overall and stage II-IIIA populations (Table 13).[27] The majority of the CNS recurrences in the osimertinib group occurred after treatment was completed.[27]

In the overall population (DCO April 2022), the HR for CNS DFS was 0.36 (95% CI: 0.23, 0.57) indicating a 64% reduction in the osimertinib arm compared with placebo (Figure 9).[27] In stage II-IIIA patients, the HR for CNS DFS was 0.24 (95% CI: 0.14, 0.42), indicating an 76% reduction in the osimertinib arm compared with placebo (Figure 10).[27]

The proportion of patients experiencing CNS DFS events was numerically lower with osimertinib compared to placebo.[27] In the overall population (DCO April 2022), CNS DFS events were experienced by 25 patients (7%) with osimertinib versus 50 patients (15%) with placebo.[27] In the stage II–IIIA population, CNS DFS events were experienced by 22 (9%) patients with osimertinib vs 41 (17%) with placebo.[27]

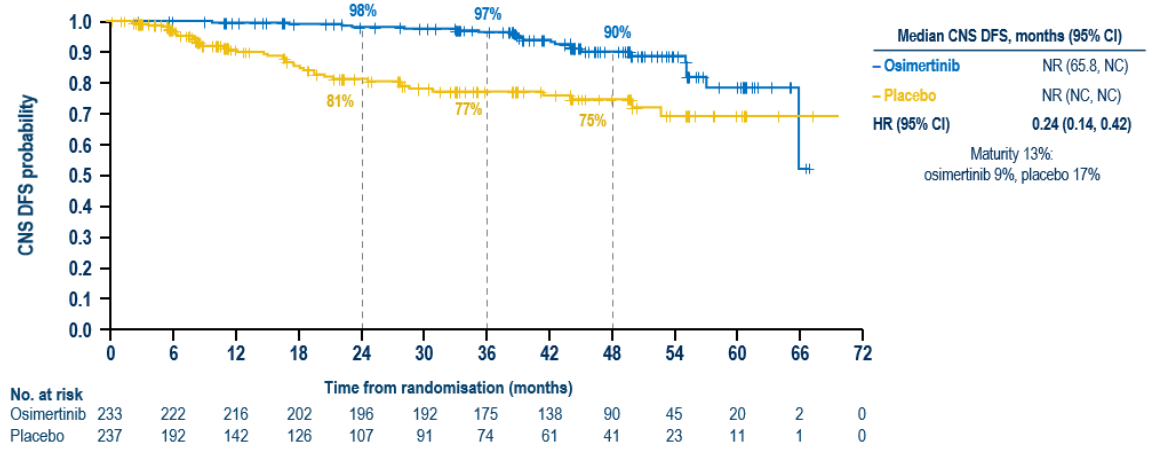
The results are consistent with the primary analysis data cut and reinforce the benefit to CNS DFS with osimertinib compared with placebo.[3,91]

Figure 9. Kaplan-Meier plot of CNS DFS in ADAURA study; overall population, post hoc updated analysis



Abbreviations: CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; NC, not calculable; NR, not reached.
Source: Herbst et al, 2023[90]

Figure 10. Kaplan-Meier plot of CNS DFS in ADAURA study; stage II-IIIA population, post hoc updated analysis



Abbreviations: CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; NC, not calculable; NR, not reached.
Source: Herbst et al, 2023[90]

Table 13. Summary of CNS recurrence or death

n (%)	Osimertinib	Placebo
Overall population		
N	339	343
Any event[a]	25 (7.4)	50 (14.6)
CNS recurrence	20 (5.9)	38 (11.1)
Death	5 (1.5)	12 (3.5)
HR (95% CI)[b,c]	0.36 (0.23, 0.57)	
Stage II–IIIA population		
N	233	237
Any event[a]	22 (9.4)	41 (17.3)
CNS recurrence	18 (7.7)	32 (13.5)
Death	4 (1.7)	9 (3.8)
HR (95% CI)[b,d]	0.24 (0.14, 0.42)	

[a] CNS DFS events defined as CNS disease recurrence or death by any cause. Disease-free survival events that do not occur within 2 scheduled visits (plus visit window) of the last evaluable assessment (or randomisation) are censored and therefore excluded in the number of events.
[b] HR <1 favours osimertinib. The HR and CI are obtained directly from the U and V statistics[98,99]
[c] This analysis was performed using an unstratified log rank test due to low event counts in the strata combinations
[d] This analysis was performed using a log rank test stratified by stage (II versus IIIA), race (Asian versus Non-Asian) and mutation type (Ex19del versus L858R). Stratification factors are as recorded in IVRS
Abbreviations: CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; HR, hazard ratio.
Source: Herbst et al. 2023[90]

Type and timing of disease recurrence

In the overall population at the final analysis (DCO April 2022), recurrence events occurred in a lower proportion of patients in the osimertinib arm than in the placebo arm (27% and 60%, respectively) (Table 14).[27] Of the patients with recurrence events in the osimertinib arm, local or regional recurrence occurred in a similar proportion of patients as distant recurrences (12% and 13%, respectively).[27] In the placebo arm, distant metastases were the most frequently-observed type of disease recurrence (31% distant and 23% locoregional).[27] Overall, treatment with osimertinib resulted in numerically fewer disease recurrences of all types compared to placebo, with 18% less distant recurrences; 13% versus 31% for each respective treatment arm.[27]

Treatment with osimertinib consistently resulted in fewer patients having disease recurrence compared to the placebo arm across the most common first sites of recurrence (Table 15).[27] The most frequently reported disease recurrence sites in both treatment arms were lung (39 patients [12%] with osimertinib and 90 patients [26%] with placebo), and CNS (22 patients [6%] with osimertinib and 39 patients [9%] with placebo).[27]

Table 14. Type of disease recurrence

n (%)	Osimertinib	Placebo
Overall population		
N	339	343
Disease recurrence[a]	93 (27.4)	205 (59.8)
Local/regional only	42 (12.4)	78 (22.7)
Distant only	45 (13.3)	107 (31.2)
Local/regional and distant	6 (1.8)	20 (5.8)

[a] DFS events not occurring within window of two scheduled visits of the last evaluable assessment were censored
Source: Herbst et al, 2023[90]

Table 15. Location of first site of recurrence (reported in >5% of patients in either treatment arm)

n (%)	Osimertinib	Placebo
Overall population		
N	339	343
Lung	39 (12)	90 (26)
CNS	22 (6)	39 (11)
Lymph nodes	19 (6)	59 (17)
Bone	13 (4)	32 (9)
Pleura	5 (1)	22 (6)

Abbreviation: CNS, central nervous system
Source: Herbst et al, 2023[90]

Overall survival

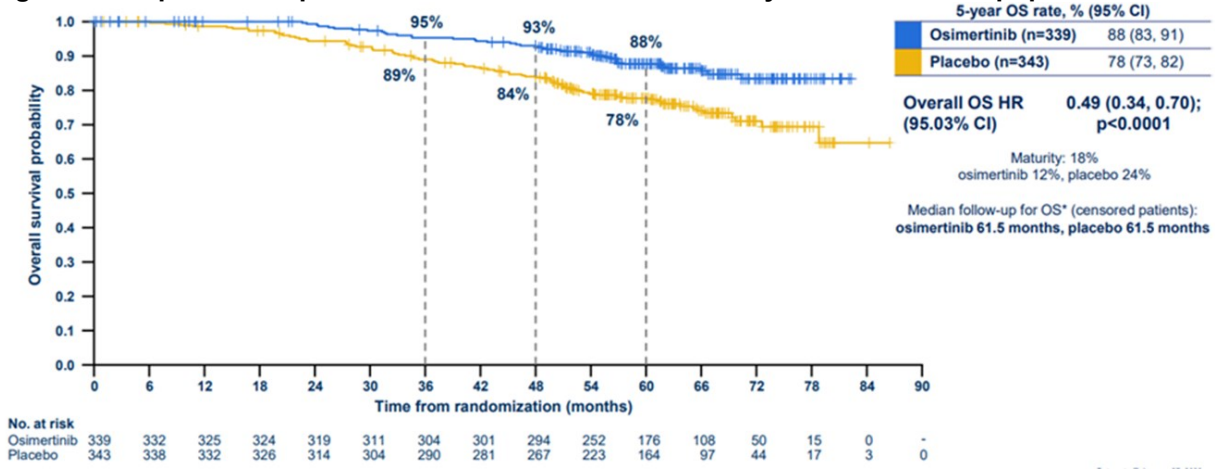
At the interim analysis (DCO January 2020) for the overall population, the maturity of overall survival (OS) data was [redacted].[91] In the subsequent final OS analysis at 5 years (DCO January 2023), the OS data had increased to a maturity level of 18%.[65]

In the overall population (DCO January 2023), treatment with osimertinib resulted in a 51% reduction in risk of death versus placebo (HR: 0.49; 95% CI: 0.34, 0.70; p<0.0001).[26] The Kaplan-Meier curve for osimertinib shows early separation from placebo that is sustained beyond 5 years (Figure 11).[65] In comparison to the placebo arm, a higher percentage of patients in the osimertinib group demonstrated survival across all evaluated time points.[93] At the 5-year landmark, 88% of patients in the osimertinib arm and 78% in the placebo arm were alive.[65]

The OS benefit was consistent between the overall and stage II-IIIA populations in the final OS analysis (DCO January 2023). In the stage II-IIIA population (with a 21% OS data maturity), 15% of patients with osimertinib and 27% with placebo had died by the final OS analysis resulting in a similar HR of 0.49 (95% CI: 0.33, 0.73) (Figure 12).[65] At the 5-year landmark, 85% of patients in the osimertinib arm were alive compared to 73% in the placebo arm.[65]

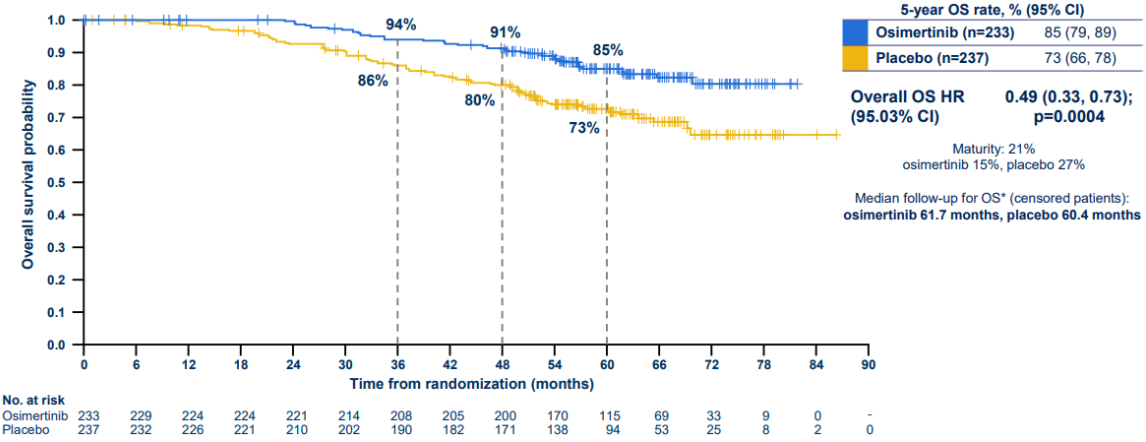
The OS data were also reviewed with clinicians interviewed in November 2023, who considered it to be positive and clinically meaningful. Similar to perceptions of the DFS data, clinicians considered the data to be generalisable to UK clinical practice while noting their lack of long-term real-world experience with this treatment.[37]

Figure 11. Kaplan-Meier plot of OS in ADAURA –final OS analysis in the overall population



Notes: DCO 27 January 2023.
Tick marks indicate censored data; Alpha allocation of 0.0497.
*Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival.
Sources: Tsuboi et al, 2023[26]; Herbst et al. 2023[90]

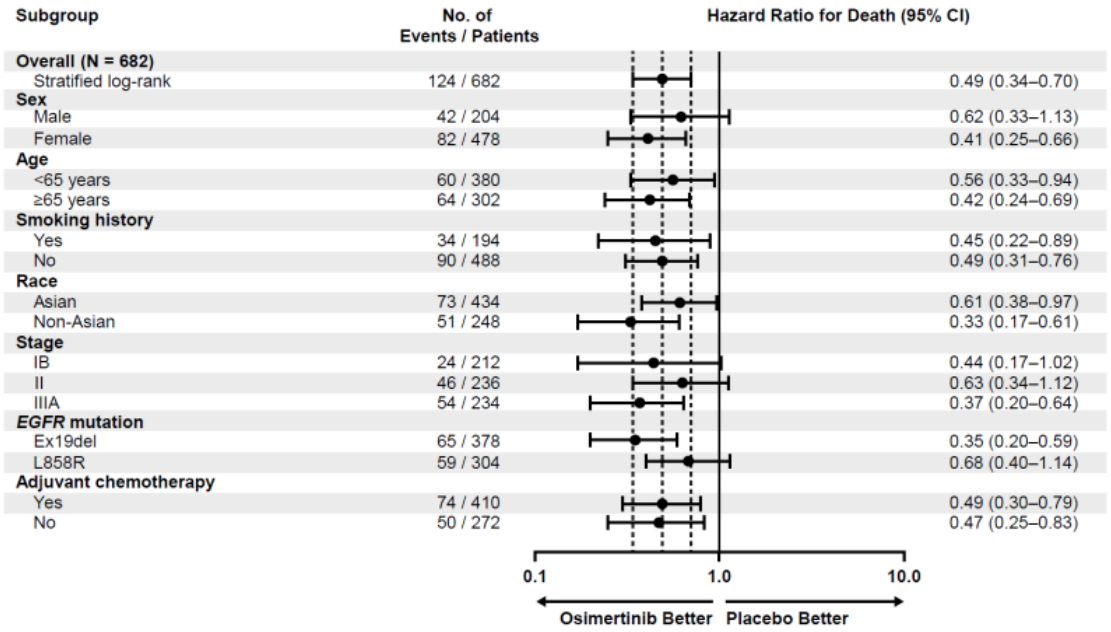
Figure 12. Kaplan-Meier plot of OS in ADAURA – updated analysis in stage II–IIIA population



DCO 27 January 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497
*Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.
Abbreviation: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival.
Sources: Tsuboi et al, 2023[26], Herbst et al. 2023[90]

The OS benefit for osimertinib over placebo was generally consistent across all subgroups (Figure 13), including those with and without prior adjuvant chemotherapy use.[26] This was confirmed by UK clinicians interviewed in November 2023.[37]

Figure 13. Subgroup Analysis of Overall Survival in the Overall Population



Notes: DCO 27 January 2023.
The subgroup analysis was performed with the use of a Cox proportional-hazards model that included treatment group, subgroup, and the treatment-by-subgroup interaction term. The middle vertical dashed line indicates the median and the outer dashed lines indicate the 95% CI for the overall HR (all patients). The CIs were not adjusted for multiplicity because the subgroup analysis was intended to show consistency of the treatment effect. A HR<1 implies a lower risk of death with osimertinib than with placebo.
Abbreviations: CI, confidence interval; DCO, data cut-off; OS, overall survival.
Source: Herbst et al, 2023[90]

B.2.6.1.3 Patient-reported outcomes

A generic HRQoL questionnaire (SF-36) was selected as the patient-reported outcome endpoint in ADAURA. The rationale for this was that patients in the adjuvant setting with no evidence of disease, such as those enrolled in ADAURA, are predominantly asymptomatic and, compared with a lung cancer-specific questionnaire, a generic HRQoL measure was considered to better capture the different aspects of physical and mental health of these patients.[100,101] SF-36 was assessed for patients on treatment every 12 weeks up to 3 years and at treatment discontinuation.

Results for SF-36 were originally collected at DCO January 2020, and were subsequently updated at DCO April 2022; the updated results are summarised here.

[redacted]

[redacted]

[redacted]

[redacted]

B.2.6.2 *SACT data*

In addition to the ADAURA trial, data on the effectiveness of osimertinib in UK clinical practice have been collected by NHS England in the Systemic Anti-Cancer Therapy (SACT) dataset. The aim of the SACT data collection was to evaluate treatment duration and OS for all patients treated with osimertinib in clinical practice. The methods and results of the SACT data are summarised below and presented in detail in Appendix R.

Between November 2021 and December 2022, data were collected for 143 patients who received adjuvant treatment with osimertinib through the CDF. Patients eligible for treatment with osimertinib through the CDF were adults after complete resection of stage IB to IIIA NSCLC (according to the 8th edition of AJCC TNM), whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

The SACT data supports the generalisability of the ADAURA trial. The characteristics were comparable for most characteristics but as can be expected, patients in clinical practice were generally older and had worse performance status than patients in the ADAURA trial. In addition, fewer patients in clinical practice received adjuvant chemotherapy prior to osimertinib compared with patients in the ADAURA trial. However, subgroup analysis from ADAURA show that osimertinib prolongs DFS and OS in patients regardless of prior adjuvant chemotherapy use, suggesting an independent treatment effect with osimertinib.[27,90]

The median follow-up time in SACT was only 6.7 months for treatment duration and 9.3 months for survival, hence the data are highly immature with heavy censoring of the KM data for both outcomes. The interpretation and use of the SACT data on treatment duration and OS are limited due to the short follow up and immature data. In addition, the level of retreatment with osimertinib in UK clinical practice, which was a key uncertainty in the original appraisal of osimertinib, was not collected through SACT.

B.2.7 *Subgroup analysis*

Please see Section B.2.6.1 for pre-defined subgroup analyses of ADAURA.

B.2.8 *Meta-analysis*

The ADAURA RCT was the only clinical trial identified that has evaluated the efficacy and safety of osimertinib as an adjuvant therapy to complete surgical resection; therefore, a meta-analysis of available evidence is not applicable to this appraisal.

B.2.9 *Indirect and mixed treatment comparisons*

Osimertinib has been studied in the phase 3 ADAURA trial where adjuvant osimertinib (with or without prior chemotherapy) is compared with placebo (with or without prior chemotherapy).[3] Established clinical management following resection in the UK reflects

the use of active monitoring with or without prior adjuvant chemotherapy, and, therefore, the appropriate comparator for osimertinib is captured in the ADAURA head-to-head trial.

In addition to established clinical management without osimertinib, the NICE final scope references adjuvant chemotherapy as a comparator for this submission. A subgroup of patients in ADAURA received adjuvant chemotherapy prior to enrolment in the trial. However, a comparison of osimertinib and active surveillance in patients who have received prior adjuvant chemotherapy is not a relevant comparison as the ADAURA trial was designed to evaluate osimertinib as an add-on therapy to standard practice in the adjuvant setting (i.e., surgery plus chemotherapy, if indicated), and not to define the optimal role of adjuvant chemotherapy in resected EGFRm NSCLC patients.[3] The introduction of adjuvant osimertinib presents a separate treatment decision, i.e. following surgery; following surgery the decision of whether to proceed with adjuvant chemotherapy is made and then a second separate treatment decision of whether to proceed with adjuvant osimertinib is made, which is not intended or expected to displace the use of adjuvant chemotherapy. In addition, it should be noted that prior chemotherapy use was not a stratification factor in the ADAURA trial and subgroups according to prior adjuvant chemotherapy use were not powered for significance.

In summary, active monitoring is the only appropriate comparator for adjuvant osimertinib as it does not displace any other treatment from the current treatment pathway, and as the appropriate comparator for osimertinib is captured in the ADAURA head-to-head trial, performing an indirect comparison is not necessary for this submission.

B.2.10 *Adverse reactions*

B.2.10.1 *ADAURA*

At the final analysis of DFS (DCO April 2022), when all patients had completed or discontinued the trial regimen, an updated safety analysis was performed of treatment exposure and adverse events (AEs).[27]The safety profile of osimertinib with extended follow-up was consistent with the results of the ADAURA primary analysis.[27]

At the April 2022 DCO, the median duration of total treatment exposure in the overall population was 35.8 months in the osimertinib group and 25.1 months in the placebo group.[27] The proportions of patients who completed the full 3 years of treatment were [redacted] in the osimertinib arm compared with [redacted] in the placebo arm.[93]

The actual median exposure in the osimertinib arm ([redacted]) [redacted] the total median exposure (35.8 months), indicating that the frequency of dosing interruptions for any reason and their median duration [redacted].[93]

B.2.10.1.1 Adverse event overview

In total, 98% of patients in the osimertinib group and 90% in the placebo group reported one or more AE during the trial (Table 16).[27] Of these, serious AEs (SAEs) were reported by 20% and 14% of patients treated with osimertinib and placebo, respectively.[27] Most reported AEs were non-serious and of mild or moderate severity. The proportions of patients with an AE leading to treatment discontinuation, dose reduction, or interruption

were low; 13%, 27%, and 12%, respectively, with osimertinib, and 3%, 1%, and 13%, respectively, with placebo (Table 16).[27]

Three deaths occurred due to an AE; 1 patient in the osimertinib arm (respiratory failure attributed to COVID-19) and 2 patients in the placebo arm (pulmonary embolism and cause unknown).[27]

The most common AEs (reported by ≥10% of patients in either treatment group) are shown in Table 17. Among patients treated with osimertinib, the most common AEs were diarrhoea, paronychia, dry skin, pruritis, and cough. The most frequently reported AEs in the placebo arm were diarrhoea, cough, upper respiratory tract infection, and arthralgia.[27] Adverse events of special interest included interstitial lung disease (ILD) and cardiac AEs. Reported ILD events occurred in 11 (3%) patients, all in the osimertinib arm and all events were mild or moderate in severity. Cardiac events (included ejection fraction decrease, cardiac failure, pulmonary oedema, and cardiomyopathy) were reported in 19 (6%) patients treated with osimertinib and 9 (3%) patients treated with placebo, most were grade 1 or 2 events.[27]

No new safety concerns were reported in the DCO of April 2022 or the final analysis (DCO January 2023) of ADAURA.[27,93]

Table 16. Summary of AEs in ADAURA

AEs, n (%)	Osimertinib (N=337)	Placebo (N=343)
Any AE	303 (98)	309 (90)
AEs considered causally-related to treatment†	308 (91)	199 (58)
AEs of CTCAE Grade 3 or higher considered causally-related to treatment	36 (11)	7 (2)
Any AE with outcome of death	1 (<1)	2 (1)
AEs with outcome of death considered causally-related to treatment†	0	0
Any SAE	68 (20)	47 (14)
SAEs considered causally reported to treatment†	10 (3)	2 (1)
Change in treatment/trial continuation due to AEs		
Trial regimen discontinuation	43 (13)	9 (3)
Dose interruption	91 (27)	43 (13)
Dose reduction	42 (13)	3 (1)

† As evaluated by the trial investigator
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.
Sources: Herbst et al, 2023[90]; Tsuboi et al, 2023[26]

Table 17. Most common AEs (≥10% of patients in either treatment group) in ADAURA

AEs, n (%)	Osimertinib (N=337)		Placebo (N=343)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	159 (47)	9 (3)	70 (20)	1 (<1)
Paronychia	92 (27)	3 (1)	5 (1)	0
Dry skin	84 (25)	1 (<1)	23 (7)	0
Pruritis	70 (21)	0	30 (9)	0
Cough	66 (20)	0	61 (18)	0
Stomatitis	59 (18)	6 (2)	15 (4)	0
Upper respiratory tract infection	53 (16)	2 (1)	37 (11)	0
Nasopharyngitis	50 (15)	0	36 (10)	0
Decreased appetite	48 (14)	2 (1)	13 (4)	0
Dermatitis acneiform	41 (12)	0	16 (5)	0
Mouth ulceration	39 (12)	0	10 (3)	0
Weight decreased	35 (10)	2 (1)	9 (3)	0
Nausea	34 (10)	1 (<1)	20 (6)	0
Rash	33 (10)	0	12 (3)	0
Arthralgia	23 (7)	0	37 (11)	0
Headache	26 (8)	0	34 (10)	0

Abbreviation: AE, adverse event.
Sources: Herbst et al, 2023[90]; Tsuboi et al, 2023[26]

B.2.10.2 *Safety overview*

As an adjuvant therapy to complete resection, osimertinib was well-tolerated in ADAURA, with no new or unexpected safety concerns identified in the final safety analysis of the trial (DCO April 2022).[27] Safety findings were largely consistent with evidence on osimertinib in previous trials in the advanced setting.[102,103]

The majority of AEs reported in ADAURA were non-serious, and of mild-to-moderate severity.[27] The proportions of patients discontinuing treatment or undergoing dose interruption or reductions due to AEs were low.[27] The most commonly reported AEs with osimertinib included diarrhoea, paronychia, dry skin, pruritis, cough and stomatitis.[27] Adverse events of special interest were ILD and cardiac events.[27] All reported ILD events were mild or moderate in severity, and no meaningful difference was observed between treatment arms for either AE of special interest.[27]

Overall, no new safety concerns with osimertinib were identified. Thus, use of adjuvant osimertinib with or without prior chemotherapy results in significant improvements in clinical efficacy outcomes with a favourable safety profile.

B.2.11 *Ongoing studies*

There are no ongoing studies for osimertinib in the indication relevant to this appraisal.

B.2.12 *Innovation*

Despite the curative intent of current treatment strategies, early-stage lung cancer is associated with poor post-surgical outcomes. Among patients who develop recurrence, median time to recurrence has been reported as 13.7 months[45] and disease recurrence rates are high (between 44% and 76% of patients develop disease recurrence or do not survive 5 years post-surgery).[13] Overall, in the past 50 years in the UK, there have been limited improvements in lung cancer survival.[28]

Patients with EGFRm NSCLC are younger have a higher likelihood of metastatic recurrence and are twice as likely to develop brain metastases and subsequent brain metastases than patients with wild-type EGFR.[15-17,36] Disease recurrence, especially brain metastasis, is associated with poor OS, a high symptom burden, detrimental effects on patient HRQoL, and considerable economic burden for the UK healthcare system.[17-21]

Before osimertinib was recommended through the CDF, the only post-resection treatment options for patients with stage IB-IIIA EGFRm NSCLC were adjuvant chemotherapy or active monitoring for patients who are ineligible or chose not to have chemotherapy. Adjuvant chemotherapy is used in some patients after complete resection with the intent to reduce recurrence and death, improving the cure rate of surgery; however, the absolute benefit is low (5-year absolute survival benefit of 5%).[13,22] Osimertinib, which was the first targeted adjuvant therapy for this population, was a step change in care where there had been no meaningful innovation for 20 years, and is now considered standard of care for patients with early-stage, resectable, EGFRm NSCLC.[88]

The results of the pivotal ADAURA trial clearly demonstrate adjuvant osimertinib is a highly innovative treatment. At the primary interim DFS analysis, osimertinib showed an unprecedented DFS benefit, alongside a reduction in CNS recurrence and an acceptable safety profile that resulted in the IDMC recommending the ADAURA trial be unblinded two years early.[89] The primary analysis results highlighted the clinical potential of osimertinib for improving post-surgical outcomes.[3]

Patients in the ADAURA trial have continued to benefit from osimertinib treatment and the recent results (DFS DCO April 2022 and OS DCO January 2023) confirm the DFS and CNS recurrence benefits are sustained and now demonstrate a significant OS benefit for osimertinib compared with placebo beyond 5 years of follow-up.[26,27] The survival benefits demonstrated by adjuvant osimertinib in this setting at later DCOs remain unprecedented and confirm this treatment as standard of care for all eligible patients.

Based on the ADAURA trial, regulatory agencies recognised adjuvant osimertinib as an innovative high impact therapy. Adjuvant osimertinib was granted FDA breakthrough therapy and was approved for use in the US under Project Orbis on the 18th of December 2020.[104] Furthermore, osimertinib was the first product granted marketing authorisation by the MHRA within Project Orbis on the 6th of May 2021.[6]

Osimertinib, a third-generation EGFR-TKI, is highly selective and capable of crossing the blood-brain barrier. First and second generation EGFR-TKIs have not demonstrated

overall survival benefit as adjuvant therapy and are not treatment options in UK clinical practice.[23,24,105-107] Additionally, first generation EGFR-TKIs do not reduce the risk of brain metastases compared with placebo.[23] In contrast, osimertinib, which can cross the blood-brain barrier, reduces the risk of CNS metastases and improves DFS and OS, thereby reducing the clinical burden for patients and the healthcare system.[26,27]

NICE has previously recognised the innovative nature of osimertinib (due to crossing blood-brain barrier, and more tolerable grade 1-2 skin-related toxicities than other EGFR-TKIs) and recommended its use in the untreated locally advanced or metastatic EGFRm NSCLC setting.[77]

B.2.13 *Interpretation of clinical effectiveness and safety evidence*

B.2.13.1 *Principal findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

B.2.13.1.1 ADAURA

At the primary interim analysis (DCO January 2020) of the randomised, double-blind, phase 3 ADAURA trial, adjuvant osimertinib, with or without prior chemotherapy, demonstrated a significant 80% reduction in risk of recurrence or death compared with placebo in patients with stage IB-IIIA EGFRm, resected NSCLC (HR: 0.20; 99.12% CI: 0.14, 0.30; p<0.001). In a post-hoc exploratory analysis, treatment with adjuvant osimertinib further resulted in significant and clinically meaningful 82% reduction in the risk of CNS recurrence compared with placebo. After 4 years of follow-up, the DFS and CNS recurrence benefits were sustained for patients who received osimertinib as an adjuvant treatment following complete resection of NSCLC. In addition, data for OS are now 18% mature and demonstrate a significant OS advantage over placebo.[26,27]

More specifically, at the final DFS analysis (DCO April 2022) in the overall population, adjuvant osimertinib reduced the risk of disease recurrence or death by 73% compared with placebo (HR: 0.27; 95% CI: 0.21, 0.34). In addition, in the overall population, the DFS benefit for osimertinib was observed across all pre-defined subgroups, providing confidence in applicability of the results to patients in the UK.[27]

Early separation between osimertinib and placebo in the Kaplan-Meier curves for DFS was reported in the primary interim analysis for both the overall and stage II-IIIA populations.[3] In the final analysis (beyond 5 years), this separation has been sustained to the last observed date in both populations.[27] Importantly, as the curves remain separated beyond the 3-year treatment period, the benefit of adjuvant osimertinib treatment is clearly maintained and demonstrates that patients benefit from adjuvant osimertinib beyond 3 years.[27]

The sustained DFS benefit is further demonstrated by the analysis of DFS rate at the final DFS analysis (DCO April 2022).[27] In both the overall and stage II-IIIA populations, the proportion of patients alive and disease free was consistently greater with adjuvant osimertinib than with placebo at all assessed timepoints [36, 48, and 60 months].[27] In the overall population at the 48-month landmark, nearly double the number of patients

treated with adjuvant osimertinib were alive and recurrence free, compared with placebo (72.7% and 37.8%, respectively).[27]

In the overall population, fewer recurrence events occurred in the osimertinib arm than in the placebo arm (27% and 60%, respectively).[27] Overall, treatment with osimertinib resulted in numerically fewer disease recurrences of all types compared to placebo, with 18% less distant recurrences; 13% versus 31% for each respective treatment arm.[27]

In the exploratory analysis of CNS recurrences in the overall population, osimertinib reduced the risk of CNS recurrence or death by 64% compared with placebo (HR: 0.36; 95% CI: 0.23, 0.57).[27] In total, the proportions of patients experiencing CNS DFS events with osimertinib and placebo were 7% and 15%, respectively.[27]

At the final OS analysis (DCO January 2023) in the overall population, adjuvant osimertinib demonstrated an unprecedented statistically significant improvement in OS; HR 0.49 (95% CI 0.34, 0.70); p<0.0001, in the overall population.[26,90] At the 5-year landmark, there were an additional 10 percentage points of patients alive treated with adjuvant osimertinib compared with placebo in both the overall and stage II-IIIA populations.[26] Moreover, the OS benefit was consistent across pre-defined subgroups in favour of adjuvant osimertinib over placebo.[26]

In the ADAURA trial, the HRQoL in patients treated with adjuvant osimertinib was maintained from baseline to 3 years.[101] Of note, in the stage II–IIIA population, more than 75% of the patients treated with adjuvant osimertinib did not experience a clinically meaningful deterioration in SF-36 physical & mental component scores or death.

The majority of AEs reported in ADAURA were non-serious, and of mild-to-moderate severity.[27] As an adjuvant therapy to complete resection, osimertinib was well-tolerated in ADAURA, with no new or unexpected safety concerns identified in the final safety analysis of the trial (DCO April 2022).[27]

B.2.13.1.2 SACT data

In addition to the ADAURA trial, data on the effectiveness of osimertinib in the adjuvant setting in UK clinical practice have been collected by NHS England in the SACT data. The aim of the SACT data collection was to evaluate treatment duration and OS for all patients treated with osimertinib in clinical practice. The methods and results of the SACT data are summarised in Section B.2.6 and described in detail in Appendix R.

Although, the treatment duration and OS results from SACT are limited due to the short follow up and heavy censoring, the patient and disease characteristics collected for UK patients receiving osimertinib in clinical practice supports the generalisability of the patient population in ADAURA (Appendix R).

B.2.13.1.3 Summary of supporting data

FLAURA

Overall survival benefit has been demonstrated with osimertinib in the phase 3 FLAURA trial compared with first-generation EGFR-TKIs (gefitinib or erlotinib) in patients with untreated, advanced/metastatic NSCLC not amenable to surgery/radiotherapy.[108] Due to

limited follow-up data for distant metastasis from ADAURA, data from FLAURA are used in the economic model as it is the key trial providing clinical data for osimertinib in the metastatic treatment setting of EGFRm NSCLC. The FLAURA trial is described in detail in Appendix M, and the results are summarised here.

The FLAURA trial showed that first line osimertinib treatment for patients with metastatic NSCLC leads to longer progression-free survival (PFS) (HR 0.46; p<0.001) and OS (HR 0.80; 95.05% CI, 0.64 to 1.00; P=0.046) compared with the EGFR-TKIs gefitinib and erlotinib.[108] The improvement in PFS and OS were observed irrespective of presence of CNS metastases at baseline.[108]

B.2.13.2 *Strengths and limitations of the clinical evidence base for the technology*

B.2.13.2.1 Strengths of the evidence base

ADAURA is the first global trial to study a third generation EGFR-TKI in the curative intent setting for resected IB-IIIA EGFRm NSCLC. It is a randomised, placebo-controlled, double-blind, multicentre trial with balanced treatment arms, and is therefore robustly designed to assess the safety and efficacy of osimertinib.

The use of a placebo control in ADAURA is highly relevant to UK clinical practice, where patients may or may not receive adjuvant chemotherapy depending on eligibility and patient choice, and are placed under active monitoring for disease recurrence.[43] The control arm in ADAURA represents what has been standard clinical management for patients in the UK in the adjuvant setting until osimertinib became available through the CDF.

The characteristics of the ADAURA trial population are considered broadly generalisable to patients with resected IB-IIIA EGFRm NSCLC in UK clinical practice, according to UK clinical experts.[37] The proportion of patients who received prior adjuvant chemotherapy in ADAURA was higher than rates of adjuvant chemotherapy in the UK, both before and after adjuvant osimertinib became available through the CDF.[14,109] However, subgroup analyses from ADAURA show that osimertinib prolongs DFS and OS in patients regardless of prior adjuvant chemotherapy, suggesting an independent treatment effect with osimertinib.[27,90]

The treatment duration in ADAURA was 3 years.[8,91] Furthermore, the benefits of osimertinib treatment have been observed in ADAURA at 4 years for DFS and 5 years for OS, including a more than 2-year follow-up period after treatment cessation, showing that the improvement in DFS compared with placebo is maintained after treatment discontinuation and that it translates to a statistically significant improvement in OS.[26,27]

Osimertinib is the first and only targeted agent to provide superior and unprecedented DFS, CNS, and OS benefits for IB-IIIA EGFRm NSCLC patients in the adjuvant setting.[26,27] Treatment with osimertinib resulted in statistically and clinically significant improvements in DFS and OS versus placebo in the ADAURA trial.[26,27] This is an important development for this patient population as there have been few developments in standard of care for NSCLC patients post-surgery over the last 20 years and recurrence rates have remained high despite curative intent treatment.[13,88] In addition,

ADAURA has shown that recurrences in patients not treated with osimertinib (placebo arm) are more frequently distant metastases whereas the frequency of locoregional and distant metastases are relatively even in patients treated with osimertinib.[27]

The significant DFS and OS benefits with osimertinib treatment observed in ADAURA, has been shown not to adversely affect patients HRQoL.[101] This further supports the benefit of osimertinib in the curative intent setting, as patients may be able to benefit from continued DFS with no detriment to QoL. In addition, the discontinuation rates of patients taking osimertinib remained low in ADAURA, and support the overall positive benefit / risk profile of osimertinib.

In ADAURA there were fewer CNS events in the osimertinib arm than the placebo arm.[27] In patients with early-stage or locally-advanced (stage IB–IIIA) EGFRm NSCLC there is a particular need to prevent distant recurrences including CNS metastases, for which EGFRm is a risk factor.[16] Brain metastases are associated with poor HRQoL, increased economic burden, and very poor survival.[18,20,110] Therefore, improved DFS with adjuvant osimertinib treatment versus standard clinical practice represents potential for a substantially reduced burden on both patients, their caregivers and the healthcare system.

The practice-changing benefits of osimertinib has made it the standard of care option in the adjuvant setting since it became available through the CDF, which was confirmed by UK clinicians interviewed in November 2023.[37] This is because the addition of osimertinib to the treatment pathway as an adjuvant therapy for patients with resectable stage IB–IIIA EGFRm NSCLC meets the substantial unmet need for a targeted, well-tolerated therapy that prevents recurrences and CNS metastases, and prolongs the overall survival after complete resection of NSCLC.

B.2.13.2.2 Potential limitations

The key limitation of the ADAURA data remains the immaturity of OS data.[26] At the time of the final DCO (January 2023) the median follow up was 60.4 months and 59.4 months for the osimertinib and placebo arm, respectively. At this timepoint, the median OS was not reached in either arm; OS data were at 18% maturity. Despite the immaturity of the data there was an unprecedented and statistically significant survival benefit with osimertinib; the 5-year OS was 88% (95% CI, 83 to 91) in the osimertinib group and 78% (95% CI, 73 to 82) in the placebo group (HR 0.49, 95% CI 0.34, 0.70; p<0.0001).

Another limitation is the length of the DFS follow up. At the final analysis (DCO April 2022), median DFS was over twice as long in the osimertinib group compared with the placebo group, at 65.8 months and 28.1 months, respectively.[27] The DFS curve for the placebo arm is starting to plateau around 48 months follow up, which indicates that after this time point, the majority of patients are at a very low risk of disease recurrence. It is expected that the DFS curve will plateau also for osimertinib, however, there is still some uncertainty around the time point of when the risk of recurrence for these patients is likely to be negligible.

Less than half of patients in the placebo arm of ADAURA received osimertinib as their first subsequent therapy for metastatic disease compared with UK clinical practice where

osimertinib is the first line treatment for over 80% of patients.[26,78] It should be noted that the ADAURA trial was designed in 2015, when osimertinib was not yet approved as a first-line treatment for metastatic EGFR-mutated NSCLC. As can be observed from the DFS curves in Figure 6, patients in the comparator arm experience recurrence events earlier than the osimertinib arm, requiring subsequent treatment choices to be made earlier. The choice of subsequent treatments may affect overall survival and the generalisability of the OS results in ADAURA to UK clinical practice. However, in the economic model subsequent treatments are based on current and expected clinical practice in the UK, and when validating the modelled survival curves with the ADAURA OS data, these have been adjusted to reflect the same distribution of subsequent therapies (section B.3.3.7).

The main limitations of the SACT data are the short follow up and therefore immaturity of the data, and the lack of a control arm, which limit the usefulness of the data. In addition, the level of retreatment with osimertinib in UK clinical practice, which was a key uncertainty in the original appraisal of osimertinib, was not collected through SACT.

B.2.13.3 *Conclusions*

There is a substantial unmet need for treatments that reduce the risk of recurrence and improve survival after complete resection of NSCLC, particularly across EGFRm NSCLC patients, because of poor prognosis and high metastatic recurrence rates.[15]

Osimertinib, a third-generation EGFR-TKI, is highly selective and capable of crossing the blood-brain barrier. The results of the pivotal ADAURA trial clearly demonstrate adjuvant osimertinib is a highly innovative treatment that provides a step change in the treatment of early-stage, resectable NSCLC, where there have been no specific therapies for patients with EGFRm NSCLC and no advancements in the adjuvant setting for NSCLC for 20 years.[2,43,88]

The findings of the ADAURA trial show unprecedented and sustained improvements in both DFS and OS with osimertinib compared with current clinical management, results which are both statistically and clinically significant for this patient population.[26,27] The DFS benefit is shown to be maintained over the 3-year treatment period of the trial, which takes patients beyond the initial period of increased recurrence risk.[27,45] The risk of CNS recurrence or death was also significantly lower with osimertinib than placebo, an important finding for this population for whom brain metastases are common[14] and associated with a heavy symptom-, HRQoL-, and economic burden.[18,20] The CNS benefit seen with osimertinib treatment is likely to contribute to the increased survival with osimertinib due to the increased severity and mortality associated with CNS recurrences. Adjuvant osimertinib treatment has been shown to lead to fewer recurrences overall, but in addition, osimertinib treatment shifts the ratio between recurrence types, decreasing the proportion of patients with distant metastases compared with locoregional recurrences, compared with placebo. Locoregional recurrences can be treated with chemoradiation, considered by UK clinicians, surveyed in 2020, to be a potentially curative option;[46] as a result increasing the proportion of patients who may achieve functional cure.

In summary, osimertinib demonstrates overwhelming efficacy as an adjuvant treatment option to complete resection with or without prior adjuvant chemotherapy, significantly improving clinical outcomes compared with active monitoring, which has been the standard of care for the last 20 years, until adjuvant osimertinib became available through the CDF.

Osimertinib meets the substantial need for a targeted, highly efficacious, well-tolerated treatment that crosses the blood-brain barrier to prevent recurrences and CNS metastases and prolongs the disease-free time and overall survival of this patient group.

B.3. Cost effectiveness

- **A cost-effectiveness analysis from the NHS and PSS perspectives was performed comparing osimertinib to placebo (active monitoring; with or without adjuvant chemotherapy) representing established clinical management before the introduction of osimertinib for the adjuvant treatment of stage IB–IIIA EGFRm-positive NSCLC after complete tumour resection**
- **In the deterministic analysis, an ICER of £18,967 per QALY was produced for osimertinib versus placebo (active monitoring), with incremental total costs of £19,870 and QALYs of 1.05. This cost-effectiveness result is below NICE's Willingness-to-Pay (WTP) threshold range of £20,000–£30,000 per QALY, indicating that osimertinib is highly cost-effective**
    - For this analysis, the list price of osimertinib (a pack of 30, 80 mg tablets) was reduced due to AstraZeneca's confidential pricing arrangement with NHS England. A PAS price of [redacted]
- **The ICER was stable across all deterministic and probabilistic sensitivity analyses**
- **The mean ICER resulting from the probabilistic analyses was comparable to the deterministic results, indicating the model was robust with respect to parameter uncertainty. At a WTP threshold of £30,000 per QALY, there is a high likelihood of osimertinib being cost-effective versus placebo (active monitoring) (76.6%)**
- **Deterministic sensitivity analyses indicated that the most influential parameter is the osimertinib DFS utility, resulting in a range of ICERs between £17,536 and £20,805 per QALY**
- **Scenario analyses that resulted in the lowest and highest ICERs are:**
    - When the cure assumption for osimertinib is started at 36 months, with a warmup period of 60 months, the ICER decreased by 39.9% to £11,405 per QALY
    - When the distributions for TP1 (DF to LR) were changed to Weibull for osimertinib and to generalised gamma for placebo, the ICER increased to £24,710 per QALY
- **Further to the important clinical benefits of osimertinib to patients, osimertinib has been demonstrated to be a highly cost-effective adjuvant treatment option for stage IB-IIIA EGFRm NSCLC after complete resection, when compared with established clinical management.**
- **Osimertinib is a highly efficacious, well tolerated treatment studied in the phase III, randomised, double-blind, multicentre ADAURA study, which was unblinded at a trial level two years early due to overwhelming efficacy (Section B.2.6.1).[3] In addition, osimertinib is an innovative treatment offering a potentially curative benefit and represents a paradigm shift to patients and healthcare providers, in a disease area with significant unmet need**
-

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 *Identification of studies*

An SLR was conducted to identify cost-effectiveness analyses in the published literature relevant to the decision problem.

Electronic databases were searched on 30 August 2023 via the OVID platform using pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and the Cochrane Library. Supplementary searches of conference proceedings were performed to identify data not captured in the database searches.

Full details of the search are provided in Appendix G. Four published studies were found that assessed the cost-effectiveness of treatments in stage IB–IIIA NSCLC following complete tumour resection with or without adjuvant chemotherapy.[111-114] A previous health technology assessment (HTA) appraisal was identified from several of these studies (Section 3.2).

B.3.1.2 *Description of identified studies*

Four unique studies were identified that reported on economic evaluations in adults with resected stage IB-IIIA NSCLC whose tumours harbour an EGFR mutation and are described in Table 18.

Table 18 Summary of Economic Evaluations identified studies

Author, Year (Country)	Population	Type of Economic Analysis	Perspective	Interventions	Model Structure	Health States	Discount Rate	Time Horizon
Lemmon et al., 2022 (US) [111]	Resected EGFR-mutated NSCLC	CEA	Healthcare perspective	Osimertinib	Markov model	Pre-progression and post-progression health states. Those were divided into CNS recurrence-positive and CNS recurrence-negative states	3% on costs and 5% on outcomes	10 years
Zhou et al., 2022 (China) [114]	Resected EGFR-mutated NSCLC	CEA	Healthcare perspective	Osimertinib	Markov model	DFS, progressed survival and death	5%	20 years
Verhoek at el, 2023 (Canada) [113]	Patients with EGFRm NSCLC after complete tumor resection (with or without prior adjuvant chemotherapy)	CEA	Healthcare perspective	Osimertinib	State transition model	Disease free, local/regional recurrence, first-line treatment for distant metastatic NSCLC, second-line treatment for distant metastatic NSCLC and death.	1.5% on costs and outcomes	38 years (lifetime)
Li et al., 2021 (China) [112]	Patients who underwent complete resection (R0) and diagnosed with stage II– IIIA (N1–N2), EGFR mutation-positive (exon 19 deletion or exon 21 Leu858Arg) NSCLC	CEA	Healthcare perspective	Gefitinib	Markov model	DFS, PD and death	3% on costs and outcomes	10 years

B.3.1.3 *Quality assessment of identified studies*

Quality assessments of included studies were conducted using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) quality checklist.[115] The assessment was done by one reviewer, which was verified by a second, senior reviewer for quality control.

All four studies reported the title, abstract, introduction and discussion per CHEERS quality checklist. Within the methods and results, there were a few items not reported; none of the studies reported whether a health economic analysis plan was developed. Furthermore, none of the studies described how the results would vary for subgroups or how the impact is distributed across different individuals. Only Verhoek et al[113] and Li et al[112] described approaches to engage external parties (patients or service recipients, the general public, communities, or stakeholders) in the design of the study. However, none of the studies reported whether external parties involvement made a difference to the approach or findings. Details of the quality assessment are available in Appendix G.

B.3.2 *Economic analysis*

The SLR did identify several existing economic evaluations of adjuvant therapy in completely resected, stage IB–IIIA EGFRm-positive NSCLC (with or without adjuvant chemotherapy). The identified studies showed an economic model in line with that of the previously submitted model (TA761). Therefore, this model was adapted and built in Microsoft Excel® to address the decision problem. The key characteristics of the model are outlined in Table 19.

Table 19. Characteristics of the economic model

Aspect	Details	Justification
Model structure	A semi-Markov state transition model, with 5 health states: disease-free (DF), locoregional recurrence (LRR), 1st line treatment for distant metastatic NSCLC (DM1), 2nd line treatment for distant metastatic NSCLC (DM2), and Death	In line with the clinical pathway for the patient population. The approach is consistent with previous NICE technology appraisals in early-stage cancer (TA107, TA424, TA569, TA632, TA671, TA876 and TA823), and the model structure was discussed and validated at an independent UK clinical advisory board in November 2020
Patient population	Completely resected, stage IB-IIIA EGFRm-positive, NSCLC, with or without adjuvant chemotherapy	Aligned with anticipated label for osimertinib and as per NICE scope
Intervention	Osimertinib	As per NICE scope
Comparator	Placebo (active monitoring)	As per NICE scope and ADAURA trial
Perspective	UK NHS and PSS	In line with the NICE reference case
Time horizon	Lifetime (37 years)	To reflect survival of the patient population: 100 years minus mean starting age (63 years)

Aspect	Details	Justification
Cycle length	4.35 weeks (1 month)	To align with recurrent costs and timing of patients' treatment, and sufficiently granular to capture events occurring during disease progression
Half-cycle correction	Applied in the base case analysis	To adjust for timing of state transitions throughout the cycle.
Discounting	3.5% for costs and benefits	In line with the NICE reference case
Clinical effectiveness – DFS	ADAURA trial	Overall population of the ADAURA trial aligns with the considered population in the model
Clinical effectiveness – locoregional recurrence	CancerLinQ (with calibration factor, see B.3.3.4)	Due to limited post-recurrence follow-up data available from ADAURA at the data cut-off (January 2023), data from the CancerLinQ database were used. A calibration factor is applied to the CancerLinQ data to adjust for population differences (in resected patients progressing to metastatic disease vs. previously untreated metastatic patients).
Clinical effectiveness – distant metastases	FLAURA trial, (with calibration factor, see B.3.3.4)	Due to limited follow-up data for distant metastasis from ADAURA at the data cut-off (January 2023), data from FLAURA is used as it is the key trial providing clinical data for osimertinib in the metastatic treatment setting of EGFRm NSCLC. A calibration factor is applied to the CancerLinQ data to adjust for population differences in resected patients progressing to metastatic disease vs previously untreated metastatic patients.

Abbreviations: EGFRm, epidermal growth factor receptor mutation; NICE, National Institute for Health and Care Excellence; NSCLC, non-small-cell lung cancer; PSS, Personal Social Services.

B.3.2.1 *Patient population*

This analysis evaluates the cost-effectiveness of osimertinib in patients with completely resected, stage IB–IIIA EGFRm-positive, NSCLC (i.e. the overall population of the ADAURA trial; baseline characteristics for the ADAURA overall trial population are shown in Table 8 and Table 9) and is therefore aligned with the published label for osimertinib:

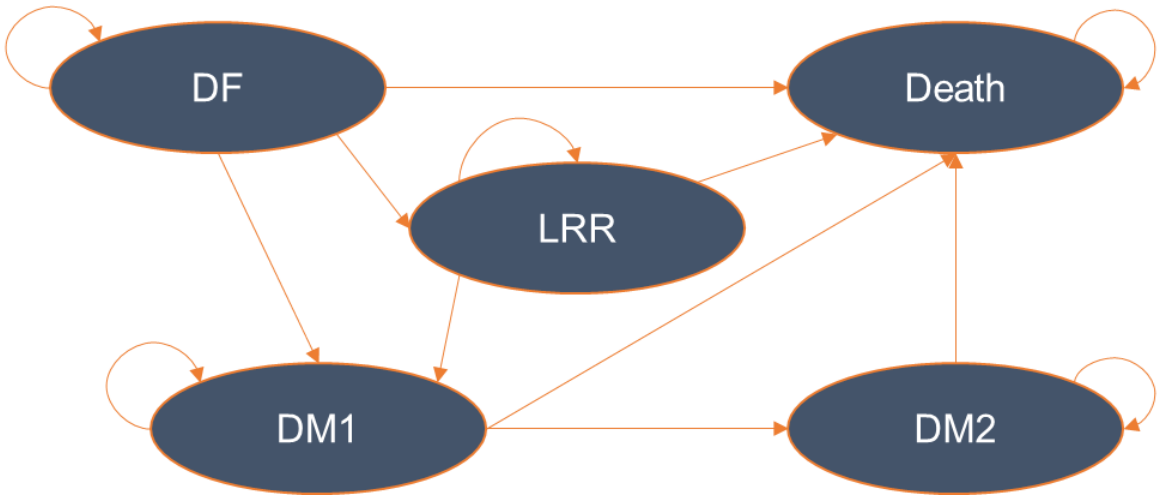
Osimertinib is recommended for use within the Cancer Drugs Fund as adjuvant treatment after complete tumour resection in adults with state IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Company evidence submission template for adjuvant osimertinib in EGFR-mutated NSCLC after complete resection.

B.3.2.2 *Model structure*

A semi-Markov model was developed in Microsoft Excel, comprising five health states that represent the disease course and survival of patients over time: 'Disease-free (DF)', 'Locoregional recurrence (LRR)', '1st line treatment for distant metastatic NSCLC (DM1)', '2nd line treatment for distant metastatic NSCLC (DM2)', and 'Death' as the absorbing state (Figure 14).

Figure 14. Economic model structure



Abbreviations: DF, disease-free; DM1, 1st line treatment for distant metastatic NSCLC; DM2, '2nd line treatment for distant metastatic NSCLC; LRR, locoregional recurrence.

The model used a cycle length of 4.35 weeks (1 month) to align with recurrent costs and timing of patients' treatment and because it was considered sufficiently granular to capture events occurring during disease progression. A half cycle correction was applied to adjust for the timing of state transitions throughout each cycle. Patients entered the model in the DF health state. The starting age (63 years) and gender distribution (70.1% female) at model entry reflected the baseline characteristics of patients in the ADAURA trial. A lifetime time horizon was applied in the base case analysis (37 years, i.e. 100 years minus the starting age of 63 years).

The analysis was performed from the perspective of the UK NHS and Personal Social Services (PSS), in line with the NICE reference case. Costs and quality-adjusted life-years (QALYs) were discounted at a rate of 3.5% per annum, as is recommended in the NICE reference case, 2013.[116] NICE guidelines also state that when a treatment cures people who otherwise eventually die and long-term health benefits are likely to be achieved, a discount rate of 1.5% for costs and outcomes can be considered.[116] As an innovative, highly effective and well tolerated treatment, offering a potentially curative benefit, osimertinib meets this description, and accordingly a scenario analysis was performed applying a discount rate of 1.5% to the cured patients for the outcomes and costs.

This type of model was considered appropriate for the decision problem, as both the structure and health states are in line with the clinical pathway outlined in Section B.1.3.3, and are consistent with previous NICE technology appraisals in early-stage cancer (TA424,[117] TA569,[118] TA632,[119] TA761[2], TA876,[69] and TA823[72]) which considered disease- or event-free health states, locoregional recurrence, successive metastatic treatment states, and death. Furthermore, the model structure was discussed and validated by clinical key opinion leaders at an independent UK

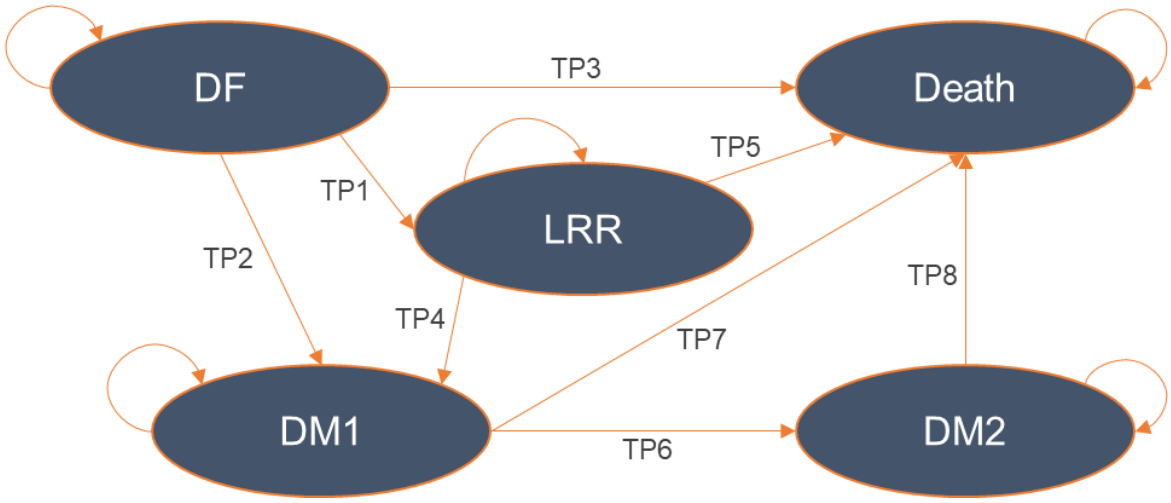
advisory board held in November 2020[87] and through a series of 1-to-1 interviews in November 2023.[37,46]

Transition between health states

Patients enter the model in the DF health state. From there, patients can transition to the LRR, DM1, or death health state (Figure 15). From the LRR health state patients can transition to the DM1 or death health state. After reaching the DM1 health state, patients can further progress to the DM2 or death health state. From the DM2 health state, patients can only transition to the death health state. The possible transitions between each of the health states are described briefly below. Full details of how the probabilities of these transitions were derived are presented in Section B.3.3.2. Table 20 lists the data sources used for each transition.

- **DF → LRR**: Disease-free patients who experience a local/regional recurrence defined as recurrence in the area of the tumour bed, hilum or mediastinal lymph nodes, transition to the locoregional recurrence health state. The transition probabilities are determined using the ADAURA trial data.
- **DF → DM1**: Disease-free patients who experience a recurrence with distant metastasis, defined as the spread of disease beyond the area of the tumour bed, hilum or mediastinal lymph nodes, will transition to the 1st line distant metastasis health state. The transition probabilities are determined using the ADAURA trial data.
- **LRR → DM1**: If, once in the LRR state, a patient's disease progresses, it is assumed they would progress to the 1st line treatment of distant metastasis health state (i.e. the event is assumed to be metastatic). Limited post-recurrence follow-up data were available from ADAURA at the 11 April 2022 data cut-off, so the probability of transitioning to this state is determined based on data from the CancerLinQ database.
- **DM1 → DM2**: After reaching the 1st line treatment of distant metastasis health state, patients whose disease progresses again transition to the 2nd line treatment distant metastasis health state. In this state patients are administered subsequent lines of treatment for their progressed metastatic NSCLC. The probability of transitioning from DM1 to DM2 is determined using the time to discontinuation of treatment (TTD) from the FLAURA trial, which is the pivotal trial of osimertinib versus SoC TKI (erlotinib/gefitinib) in the metastatic setting. This trial was used due to limited, immature post-DFS and overall survival data available from ADAURA. FLAURA patients were mostly previously untreated metastatic patients, whereas ADAURA metastatic patients had received prior radical treatment. The impact that this difference in populations has on the model is explored in section B.3.3.4.
- **Transitions to death (**DF → Death; LRR → Death; DM1 → Death; DM2 → Death): Death is an absorbing state. Patients can transition to death from any health state in the model. Within each model cycle, all transition probabilities to death were constrained to be at least as high as background population mortality, as estimated from UK lifetables, based on the years 2018 to 2020, given the age and gender distribution of the cohort during the cycle period.[120]

Figure 15. Economic model structure with transitions



Abbreviations: DF, disease-free; DM1/2, 1st/2nd line treatment for distant metastatic NSCLC; LRR, locoregional recurrence; TP, transition probability.

Table 20: Overview of the data source used per transition

Transition	Data source
TP1: DF → LRR	ADAURA[27]
TP2: DF → DM1	ADAURA[27]
TP3: DF → DEATH	UK life tables[120]
TP4: LRR → DM1*^	CancerLinQ[121]
TP5: LRR → DEATH	UK life tables[120]
TP6: DM1 → DM2*	FLAURA[100]
TP7: DM1 → DEATH	FLAURA[3 100]/ UK life tables[120]
TP8: DM2 → DEATH*	FLAURA[100], IMPower150[122]

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis, LRR, locoregional recurrence.
*A calibration factor is applied to this transition, see section B.3.3.4
^Pooled analysis of data from both treatment arms

B.3.2.3 *Intervention technology and comparators*

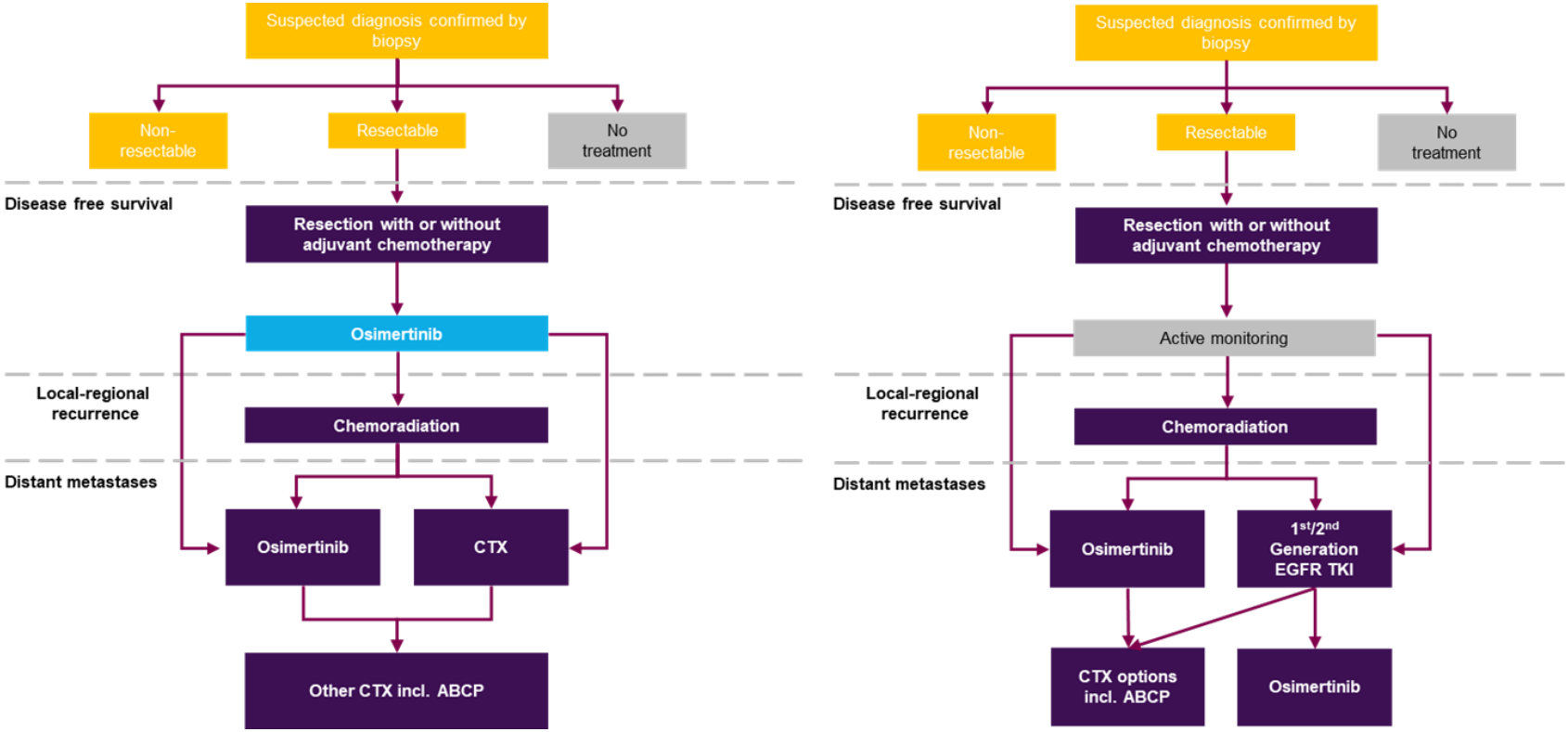
The ADAURA trial is the key data source of this cost-effectiveness analysis, in which osimertinib (intervention arm) is compared with placebo (comparator arm) in patients with completely resected, stage IB–IIIA EGFRm-positive NSCLC with or without adjuvant chemotherapy.

Osimertinib is an innovative treatment for the indicated patient population and is administered orally at a dose of 80 mg once daily for 3 years.

In line with the NICE decision problem and the ADAURA trial, the comparator for this analysis is placebo (established clinical management without osimertinib; that is, active monitoring). Data for the comparator in the disease-free state are taken from the placebo (active monitoring) arm of the ADAURA trial which appropriately reflects UK clinical practice without osimertinib. As described in Section B.3.2.3, active monitoring is the only appropriate comparator for adjuvant osimertinib. Adjuvant chemotherapy is not considered to be an appropriate comparator, given that adjuvant osimertinib is not intended to displace adjuvant chemotherapy but provide an additional option for further adjuvant therapy after the patient/clinician decision to receive/administer adjuvant chemotherapy following complete resection.

Following the initial therapies (i.e. osimertinib, as intervention, or active monitoring only, as comparator), once patients progress from DF state, the treatments outlined in Figure 16 are considered in the model based on current and expected clinical practice suggested and validated by UK clinicians. A detailed description of the treatment sequence is provided in Section B.3.5.2.1.

Figure 16. Treatment sequence applied in the model per osimertinib and placebo (active monitoring) treatment arms



Abbreviation: CTX, Chemotherapy; TKI, tyrosine kinase inhibitor

Further information on the costs and resource use associated with the intervention, comparator 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 19 and Table 20, the primary data source used to populate the clinical elements of the cost-effectiveness model was the pivotal phase III ADAURA trial of osimertinib vs placebo (active monitoring) after resection and optional adjuvant chemotherapy.[27] As limited post-recurrence follow-up data were available from ADAURA at the 11 April 2022 data cut-off, parametric survival modelling was used to estimate the probability of transition in post-DFS health states. For LRR to DM1 data from CancerLinQ, a US real-world evidence database comprising over 1.4 million patients with a primary cancer diagnosis (Appendix M.2) was used.[123] The transition probabilities from the distant metastases health states (DM1 and DM2) are primarily estimated from the FLAURA phase III trial, which evaluates osimertinib versus the standard of care (gefitinib or erlotinib) as first-line treatment in patients with advanced EGFRm-positive NSCLC (Appendix M.1).[124] The FLAURA trial was the primary source of survival data used to inform the efficacy of treatment in the metastatic setting in TA654.[77]

Where the risk of deaths from these trials from the respective health states was lower than or equal to that of the general population mortality, the risk of death was considered equivalent to the general population and general population mortality was applied using UK National Life Tables 2018-2020.[120]

Both the trial populations and the estimated survival outcomes included in the model, including the use of ADAURA, CancerLinQ (for the LRR to DM1 transition) and FLAURA (for the DM1 and DM2 transitions), were validated in the November 2020 survey of six UK clinicians (henceforth called the '2020 survey'). In the November 2023 series of 1-to-1 interviews with five UK clinicians (henceforth called the '2023 interviews') the ADAURA and FLAURA data were re-validated.[37,46] Clinical experts noted that the overall trial population observed in ADAURA is representative of patients with stage IB–IIIA EGFRm-positive NSCLC who could expect to receive adjuvant osimertinib in the UK. As a result, responses and outcomes seen in this study are assumed to be reflective of UK clinical practice. In addition, the UK clinicians were satisfied that the data sourced from CancerLinQ for the LRR to DM1 transition, and from FLAURA for the DM1 and DM2 health states, were also appropriate and generalisable to this patient population in the UK.[37,46] To evaluate and further validate the survival outcomes estimated by the multi-state model, the aggregated DFS and OS curves produced by the model were compared with the Kaplan-Meier DFS and OS endpoints of ADAURA (Section B.3.3.7).

Data on overall survival was available from the Systemic Anti-Cancer Therapy (SACT) dataset, however, with a data maturity of 6.2% (9 events out of 143 patients) and a median follow-up of 9.3 months, incorporating this data into the model was deemed inappropriate, as described in section B.2.6.2.

B.3.3.1.1 Survival analyses and extrapolation

Survival analyses were conducted according to the following steps, which are aligned with standard practice and guidance from the NICE decision support unit (DSU):[125]

1. Assess the proportional hazards assumption
2. Fit parametric functions to data for each transition

3. Assess goodness of fit of each transition through visual inspection of the KM curves, and Akaike Information Criterion (AIC)/ Bayesian Information Criterion (BIC) statistics

4. Assess observed hazards and hazards predicted by the models overtime

Once this process was followed for all individual transitions, and given the multi-state model structure, the fit of the aggregated DFS and OS curves compared to the KM curves from the trial were externally validated with clinicians.

More detail of these steps is provided below.

Assessment of the proportional hazards assumption

Prior to deciding on the most appropriate parametric distribution, it is important to check whether the proportional hazards (PH) assumption holds. The PH assumption states that the hazard in one group (arm A) is a constant proportion of the hazard in the other group (arm B). That is, although the hazard may vary with time, the ratio of the hazard rates is constant. The PH assumption can be tested both graphically and statistically using the Schoenfeld residuals test and the cumulative hazard plot.[125] The Schoenfeld residuals graph plots time on the x-axis versus the Schoenfeld residuals on the y-axis, whereas the log hazard graph plots time on the x-axis vs the log(Survival) on the y-axis. The PH assumption can be assumed to hold if the plot of the residuals against time should show a linear trend with slope=0 and/or the log hazard plot shows a linear trend between the treatment arms. A p-value is also generated as the result of a test of non-negative slope. If the PH assumption holds, combined fits (where the same distribution is fitted to both arms, with a treatment effect on the active arm), and individual fits (where each arm is fitted to a separate distribution) can be used. Where the PH assumption is violated, single dependant models are not a viable option and separate parametric models (individual fits) must be used.

Parametric extrapolation methods and selection

In accordance with standard practice and guidance from the NICE decision support unit (DSU), a parametric extrapolation function was fitted using a frequentist approach to the datasets from the studies outlined in Table 20. Several candidate distributions were fit to the data and assessed for “goodness of fit”, based on visual inspection and on AIC and BIC statistics. The selected distribution provides the basis of the extrapolation beyond the observed follow-up period relevant to the source data. In line with NICE DSU Technical Support Document (TSD) all standard parametric functions (exponential, Weibull, log logistic, lognormal, generalised Gamma and Gompertz) were explored.[125] Flexible survival extrapolations covered by NICE DSU TSD 21 were not run as the semi-Markov model structure combined with a landmark cure approach was considered to provide sufficient flexibility.[126]

The within-trial and extrapolated hazards were assessed for each individual transition. For the within-trial period, the (Kernel) smoothed hazards from the trial were visually compared to the model-predicted hazards for TP1 and TP2 (i.e., informed by the ADAURA trial), as these are relative immature.

Fit of aggregated curves

As described by Williams et al, 2017, in multi-state models, in which competing risks are involved, survival is based on a compound of two or more hazards rather than just one and thus the hazard

of a particular event cannot simply be derived from the probability of the survival.[127] State occupancy probabilities are defined by the hazards for each transition into that particular state. It should be noted that in multi-state models where competing risks are applied, the goodness-of-fit statistics for individual transitions do not by definition correspond to assessing the state occupancy probabilities that are ultimately of interest.[127] The individual distributions for the transition probabilities were selected based upon both visual inspection and AIC/BIC, and afterwards, the resultant model was evaluated based upon a visual inspection of the combined DFS and OS curves. The final model had to pass both visual inspection for the aggregated curves and statistical fit of individuals TPs, otherwise clinically plausible alternatives for the individual transitions were re-evaluated and the process repeated.

The fit of the aggregated curves and selected key extrapolations were validated by clinicians in the 2023 interviews.[37]

B.3.3.2 *Transition probabilities*

To derive the transition probabilities for a multi-state model (MSM), competing risks must be considered. When competing risks are present, there is no longer the one-to-one relationship between the hazard and survival probabilities that there is in the absence of competing risks. That is to say, the hazard of a particular event cannot simply be derived from the probability of survival, because death may occur from any one of a number of hazards, rather than just one.

Therefore, the transition probabilities of leaving a health state are derived by calculating the total probability of leaving that health state and assigning a proportional probability to each transition. The total probability is calculated by using the sum of the hazards of the transitions as the rate of the exponential distribution. The resultant probability can then be divided to each transition proportionately to their hazard. For DFS this would be:

Total probability = exp(- sum[hazard TP1 + hazard TP2 + hazard TP3])

Transition probability TP1 = hazard TP1 / sum(hazard TP1 + hazard TP2 + hazard TP3) * Total probability

B.3.3.3 *Modelling of DFS (TP1 to TP3)*

Patients start in the DF health state and remain there if they do not experience disease recurrence or death. The probability of remaining in the DF health state is derived from patient-level data in the ADAURA study. The KM estimate of median duration of DFS in the osimertinib arm was 65.8 months (95% CI: 61.7, non-calculable [NC]) compared with 28.1 months (95% CI: 22.1, 35.0) in the active monitoring arm.[92] At the time of second data cut-off (April 2022), 100% of patients in the overall trial population had been followed for at least three years. For TP1 and TP2, parametric functions were applied to patient-level ADAURA data to facilitate extrapolation beyond the follow-up period, as per NICE DSU 14 guidance.[125] These extrapolations formed the basis of the transition probabilities in the model. However, since the ADAURA study uses DFS and OS as endpoints, the competing risks methodology described by Williams et al, 2017, was also applied to generate the transitions used in the model.[127]

Note that for the transition from DF to Death (TP3), the number of recorded events in ADAURA was insufficient to fit to any distribution, and therefore this transition was modelled based on the background mortality of the age-adjusted UK population.

B.3.3.3.1 Cure assumption

There is the potential for functional cure in the patient population considered in this economic evaluation. Therefore, a cure assumption was included in the model to capture the expected functional cure or long-term remission of these patients beyond the currently available follow up DFS data from ADAURA. The rationale supporting this important component is outlined below.

Clinical data and context

Complete surgical resection represents a potentially curative pathway for early-stage NSCLC and it is expected that adjuvant treatment with osimertinib will increase the proportion of patients cured. Adjuvant osimertinib has been demonstrated to statistically significantly reduce the risk of post-surgical disease recurrence vs placebo (active monitoring), which is predicted to result in a reduced risk of disease progression and death. Therefore, it is important that the economic model captures the long-term clinical benefits associated with osimertinib and enables comparison with current standard of care, that is active monitoring alone.[3,89] During interviews, clinicians stated that they expected the significant DFS benefit with osimertinib in the ADAURA trial to translate to a greater proportion of osimertinib-treated patients achieving cure, compared with placebo (active monitoring).[46]

When considering the reduction in disease recurrence observed with osimertinib in ADAURA, 12% of the osimertinib group and 23% of the placebo (active monitoring) group had locoregional recurrence, while distant metastatic recurrence occurred in 13% of the osimertinib group and 31% of the placebo group.[27] Thus, if a patient does experience recurrence when treated with osimertinib, the patient is more likely to have a locoregional recurrence instead of a distant metastatic recurrence, whereas SoC patients are more likely to get distant metastatic recurrence. Treatment options at the locoregional pathway include radical treatment (chemoradiation). The risk of central nervous system (CNS) recurrence or death which, as outlined in Section B.3.5.3 is associated with increased treatment costs and further decreased quality of life, was also significantly reduced by 64% with osimertinib in the overall population (HR: 0.36; 95% CI: 0.23, 0.57). Thus, the reduction in distant metastases is an important clinical benefit of osimertinib, that suggests improved survival and a potential for cure vs active monitoring.

Previous NICE appraisals

A search was conducted for NICE oncology appraisals that have previously used a cure assumption to develop economic models. In the (neo-)adjuvant setting, three early lung cancer appraisals (TA761, TA823 and TA876), two early breast cancer appraisals (TA569, TA632) and one melanoma appraisal (TA553) were identified that explicitly modelled cure.[2,69,72,118,119,128] Two non-adjuvant appraisals were identified in leukaemia (TA554 and TA450) that also explicitly modelled cure.[129,130] In TA554 and TA450, patients in the event-free or initial health state were assumed to be functionally cured at Year 5 and Year 4, respectively, and after this timepoint patients were expected to be no longer at risk of disease recurrence and subject only to background general population mortality. The rationale for the cure assumption in both appraisals was mostly based on expert clinical opinion. In TA569 and TA632, the rationale for the cure assumption was based on external data. In the committee's preferred base case, a linear increase in cure rate was applied at Year 3, which reached a maximum cure rate of 95%. The ERG and committee's clinical experts agreed that, despite the robust clinical data to support the assumption of cure, a maximum 95% cure rate was appropriate and that a 100% cure rate was clinically

implausible. In TA761, the committee had a preferred assumption of an 8-year cure timepoint for the treatment arm to reflect the possible delay of recurrence after treatment, rather than prevention.

Published literature

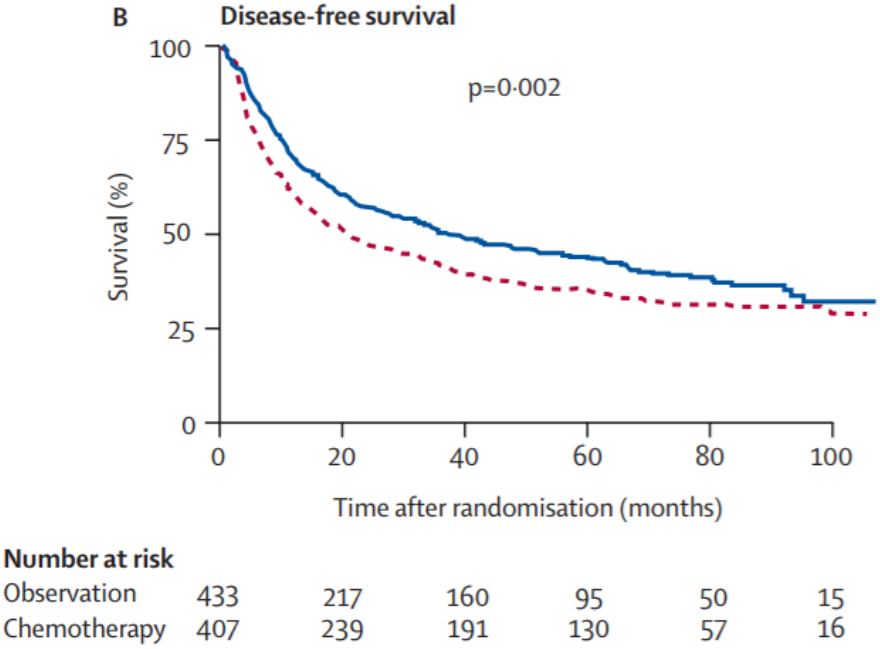
To further support the assumption of functional cure in the economic analysis, a targeted literature search was conducted to identify published studies evaluating long term DFS rates (> 3 – 4 years) in patients with early stage (stage I-III) NSCLC following complete surgical resection. Although published data on longer-term survival outcomes in this setting are limited – particularly in stage IB–IIIA EGFRm-positive NSCLC – several studies[13,131,132] were identified in patients with completely resected stage IB–IIIA NSCLC. These studies indicate that the underlying risk of disease recurrence in the earlier follow-up period (noted as less than 36–48 months) is not representative of the risk of recurrence at later time periods.[13,131,132] Generally, patients who are disease-free following complete tumour resection appear to be exposed to a far higher risk of recurrence early in the follow-up period, with the risk of recurrence decreasing over time.

It is important to note that the extrapolation of DFS data from the ADAURA trial to derive the transition probabilities applied in the cost effectiveness model are based on a 69 month time period in which the placebo arm clearly experiences a plateau, however, the interpretation of the adjuvant osimertinib DFS curve beyond 48 months is limited due to censoring and low number of patients at risk, but is also expected to reach a plateau indicating patients are at low risk of recurrence. As a result, the parametric models do not capture the full extent of the expected plateau in the osimertinib arm, and the extrapolated DFS curves from ADAURA are likely to overestimate the long-term rate of disease recurrence. This is in line with opinion of interviewed clinical experts who suggested that the extrapolated ADAURA DFS curves were pessimistic for an early-stage resected patient population in the 2020 survey (Section B.3.3.8).[46]

One trial was identified that provided long-term DFS outcomes in early stage resected NSCLC. The ANITA study was a phase II, open-label, multicentre RCT that compared adjuvant vinorelbine plus cisplatin vs observation in patients with completely resected stage IB–IIIA NSCLC.[132] In total, 840 patients were enrolled and randomly assigned to observation or 30 mg/m^2 vinorelbine plus 100 mg/m^2 cisplatin. Disease stage and WHO performance status at baseline were comparable with the population enrolled in ADAURA, although there were differences between the two studies in proportion of gender, type of surgery and tumour histology (table of patients' baseline characteristics is presented in Appendix P).

After a median follow-up of 76 months in the chemotherapy arm and 77 months in the observation arm, median OS was 65.7 months (95% CI: 47.9, 88.5) and 43.7 months (95% CI: 35.7, 52.3), respectively. Median DFS was 36.3 months (95% CI: 28.0, 52.1) in the chemotherapy group and 20.7 months (95% CI: 16.1, 28.6) in the observation group. However, regardless of treatment arm, there appeared to be a plateau in the DFS curve from approximately 48–60 months' follow-up (Figure 17), suggesting that after this timepoint, the majority of patients are no longer at risk of disease recurrence, and thus providing further support for a functional cure in this patient population and is consistent with what we see in ADAURA.

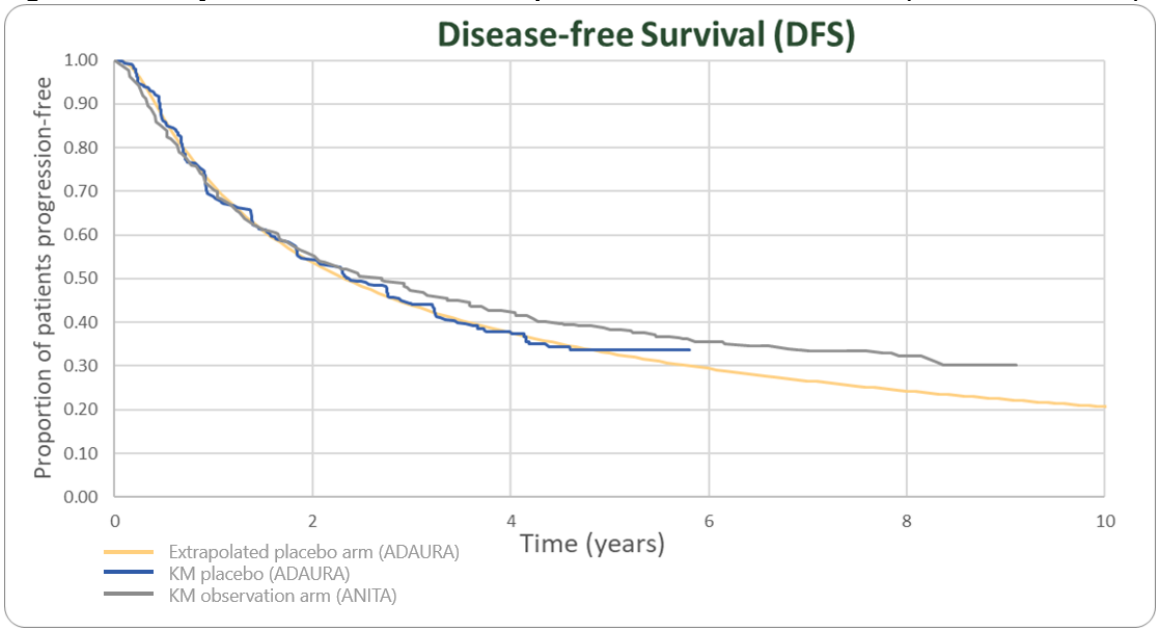
Figure 17. ANITA study DFS



Abbreviations: DFS, disease-free survival.
The blue line denotes the chemotherapy group; the red dotted line denotes the observation group.

To explore this further, pseudo-patient level data were derived from the KM DFS curve of the observation arm of the ANITA study using the algorithm developed by Guyot et al, 2012.[133] This dataset was extrapolated and compared alongside the best fitting combined extrapolated DFS curves from the ADAURA placebo (active monitoring) arm (TP1 [DF to LR]: lognormal; TP2 [DF to DM1]: lognormal), see Section B.3.3.7) using the final DFS DCO (2022) since both patient groups received similar treatment regimens in their respective trials and is a more relevant comparison than data from the chemotherapy arm of ANITA (see Figure 18 below). Applying a 0% cure proportion in the ADAURA placebo (active monitoring) arm (patients are still at risk of recurrence) suggests that the risk of disease recurrence beyond 60 months may be overestimated in the ADAURA placebo (active monitoring) arm when compared with the observed long-term DFS data from the ANITA study cohort. Therefore, it is plausible to assume that the extrapolated disease recurrence in osimertinib-treated patients is also overestimated and that implementing a cure assumption is justified.

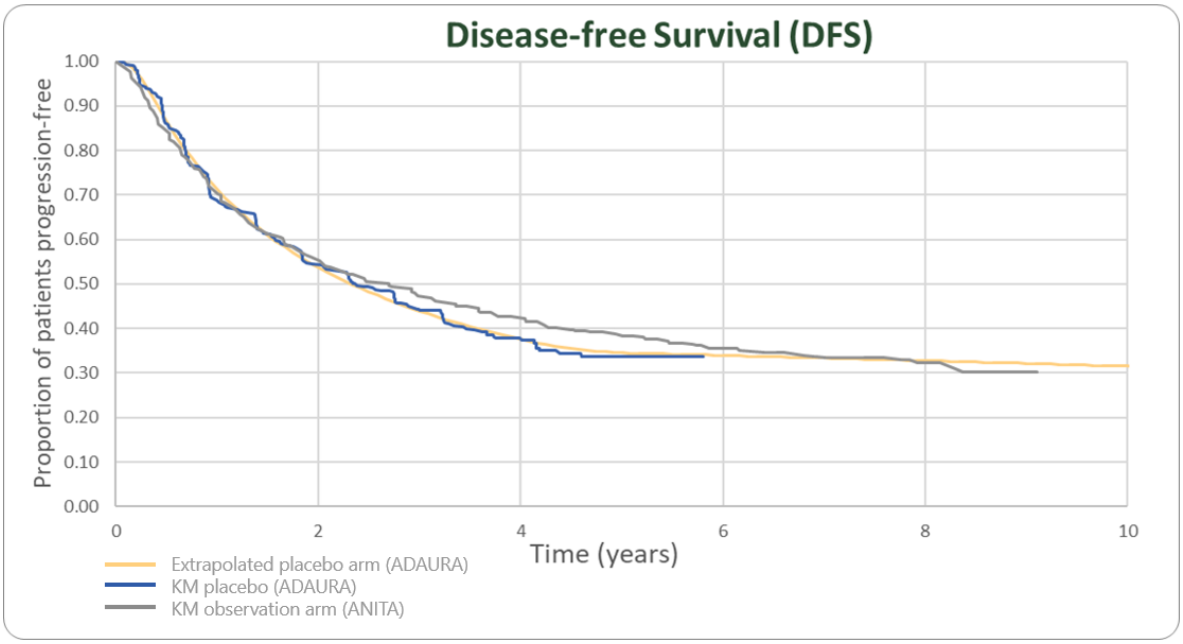
Figure 18. Unadjusted ADAURA DFS extrapolations versus ANITA DFS (no modelled cure)



Abbreviations: DFS, disease-free survival; KM, Kaplan-Meier.

Conversely, when a cure rate starting from year 4 with 0% to the start of year 5 with 95% was applied to the active monitoring arm, the predicted DF rates from the ADAURA active monitoring arm were more consistent with the longer-term DF KM curve from ANITA (see Figure 19).

Figure 19. Adjusted ADAURA DFS extrapolations versus ANITA DFS (95% cure proportion at 5 years)



Abbreviations: DFS, disease-free survival; KM, Kaplan-Meier.

Further statistical analyses were also considered to estimate a plausible rate of cure in patients with stage IB–IIIA surgically-resected NSCLC. Mixture-cure models (MCM) were not explored using the ADAURA data due to the combination of relatively low data maturity (45% overall maturity) and heavy censoring after 48 months.[27] That MCMs are usually less fit to be applied directly to an RCT is also recognised in NICE DSU TSD 21 ("In small datasets there may be issues around the practicality and plausibility of being able to reliably estimate the cure fraction").[126] Instead, MCMs were fitted to the pseudo-patient level DFS data from the placebo (active monitoring) arm of the ANITA trial. The MCM analysis was performed using the flexsurvcure package in R.[134] Overall the MCM analysis estimated cure fraction rates ranging from 4–35% and predicted DFS rates at 5 years of 33–35% for the ANITA trial (see Table 21). Using the landmark method in the cost-effectiveness model at 5 years, the estimated rate of cure for the placebo (active monitoring) arm of ADAURA is comparable to the range estimated in this analysis (Table 21), calculated by applying the 5-year DFS (29.7%) with the 95%-cure for an estimated cure of 28.2%. This supports the validity of the model extrapolations, and the use of the landmark method to predict cure.

Table 21. Estimated cure fraction rates and DFS five-year rates using mixture cure models applied to the ANITA trial

Model	AIC	Cure fraction (%) estimated from ANITA	DFS at 5 years (%) from the ANITA trial extrapolations
Generalised Gamma	2628.17	15.6 (4.0, 45.1)	34.6
Lognormal	2635.82	27.9 (22.7, 33.8)	33.9
Loglogistic	2646.56	27.3 (22.1, 33.2)	33.8
Gompertz	2667.83	22.9 (9.5, 45.9)	33.9
Exponential	2673.97	30.6 (26.0, 35.5)	33.3
Gamma	2675.12	30.8 (26.3, 35.8)	33.2
Weibull	2675.93	30.5 (25.8, 35.5)	33.3

Abbreviations: AIC, Akaike information criterion; DFS, disease-free survival.

Feedback from KOLs and clinical practice

The 2020 survey and 2023 interviews confirm that in UK clinical practice, patients with completely resected early-stage NSCLC are typically discharged from care after five years if they have not experienced disease recurrence.[46] Patients are at greatest risk of recurrence 18–24 months post-surgery and therefore if patients remain disease free at five years they can be considered functionally cured. This was also reported in a published Delphi consensus on DFS in NSCLC.[73] Clinicians generally consider the risk of recurrence to be very low after five years, with the risk of recurrence reducing as time since surgery increases. In addition, interviewed clinicians advised that, in patients who are disease free at five years and have been discharged from the service, it is reasonable to assume that survival is similar to that of the general population (given that these patients may now be considered functionally cured).[37,46]

Therefore, the time point after which patients are considered cured in the active monitoring arm of the model was 5 years.

For the osimertinib arm, this was extended to 8 years following the suggestions from the ERGs clinical advisors in the previous submission (TA761) that adjuvant osimertinib may delay relapse rather than prevent it.[2] Therefore, the treatment duration of 3 years was added to the 5-year cure time point of the active monitoring arm.

This is a pessimistic approach, as clinical experts in the 2020 survey were divided between a 5 and 8 year cure time point for osimertinib, and the 2023-interviews showed a similar outcome; 3 out of 5 clinicians agreed that the 36 month treatment period for osimertinib should be accounted for whereas 2 out of 5 clinicians preferred that the cure time point should be 5 years in both arms, as there is no rationale why cure on the osimertinib arm would be later than in the active monitoring arm. [37,46]

The clinicians also agreed that a gradually increasing percentage of patients could be assumed to be functionally cured before the five-year treatment-free mark is reached. Therefore, when applying 'cure' in the model, a gradual increase was modelled, henceforth described as a "warm-up period". In the active monitoring arm, this was modelled as patients being 0% cured after 48 months (4 years), increasing to 95% after an additional 12 months (5 years total). For the osimertinib arm, patients were 0% cured after 48 months, increasing to 95% in an additional 48 months to compensate for the 36 months of osimertinib treatment (8 years total).

Summary and approach used in the model

A cure assumption was included in the economic analysis based on expert clinical opinion, ADAURA clinical data and supporting evidence from the published literature and previous NICE technology appraisals (i.e. TA761[2], TA876[69], and TA823[72]). Clinicians also stated that they expect the significant DFS benefit with osimertinib in ADAURA to translate to a greater proportion of osimertinib-patients being cured, compared with placebo (active monitoring).[46] Indeed, as described in Section B.2.12, the ADAURA trial was unblinded two years early on recommendation from the IDMC, due to the overwhelming efficacy of osimertinib (unprecedented improvements in DFS and a significantly lower risk of CNS recurrence or death compared with placebo (active monitoring)).[3] As functional cure has been well established as a realistic outcome for patients receiving active monitoring after surgery following the ANITA trial, the interviewed clinicians and previous appraisals, not including a cure assumption for the osimertinib -arm would therefore be overly pessimistic.[46]

In the base case analysis 95% of patients in the DF health state were assumed to be functionally cured after 5 years in the active monitoring arm, and after 8 years in the osimertinib arm to account for the 36 months of osimertinib treatment. Patients who were cured were deemed to no longer be at risk of disease recurrence; these patients were instead subject to age-matched general population mortality. Once a patient was considered functionally cured (i.e., at the 5-year time point for active monitoring, and the 8-year time point for osimertinib), health state costs were not incurred (as patients would be discharged and not monitored), and health state utility was maintained at the same value as for patients in the DF state prior to the cure point (since average HRQoL is not expected to differ among DF patients). The application of this method was also deemed necessary to better reflect functional cure in the model; selecting the best clinically plausible (based on functional cure expectations) and statistically fitting survival curves for transition probabilities in the DF state, which underlies the overall DFS curve, were not considered

fully reflective of survival outcomes anticipated by clinicians. Clinicians also found that the application of a warm-up period was more plausible rather than assuming an immediate application of the cure assumption from 5 years.

Despite the arguments outlined above, uncertainty around the cure assumption was tested in scenario analyses. Scenarios tested included applying different cure timepoints and varying the percentage of patients cured.

B.3.3.3.2 TP1: Disease-free (DF) to locoregional recurrence (LRR)

KM data

For the model's DF to LRR transition, KM data for the time to locoregional recurrence from the ADAURA trial was used (Figure 20). Parametric curves were fitted to the data, and the curve selection was based on the methods described below.

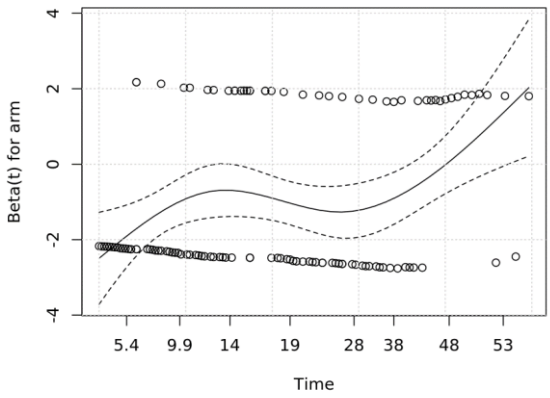
Figure 20. KM curves for time to locoregional recurrence in the osimertinib and placebo (active monitoring) arms of ADAURA

Abbreviation: KM, Kaplan-Meier.

Assessment of the proportional hazards assumption

Figure 21 presents the cumulative hazards plot and the Schoenfeld residuals plot for the transition DF to LRR. The Schoenfeld residuals plot and the Schoenfeld residuals test (p=0.003) indicate that the proportional hazards assumption is violated. Therefore, only individual fits were considered in the model.

Figure 21. Schoenfeld residuals and cumulative hazard plot for the transition DF to LRR (TP1)



[redacted]

Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DF, disease-free; LRR, locoregional recurrence.

Selection of base case parametric distributions

Parametric distributions fit separately to each trial arm were selected based on their goodness of fit statistics, visual inspection and consideration of whether the extrapolation was clinically plausible.

Table 22 presents the AIC and BIC statistics, which shows lognormal provides the best within-trial fit for osimertinib, although all distributions fall within 5 points of each other. For active monitoring, lognormal and generalised gamma provide the best within-trial fit.

Table 22. AIC and BIC values for the fitted distributions to the transition DF to LRR

	Osimertinib			Placebo (active monitoring)		
Model	**Clinically viable**	**AIC**	**BIC**	**Clinically viable**	**AIC**	**BIC**
Exponential	Yes	572.92	576.75	Yes	913.12	916.96
Weibull	No	568.98	576.63	Yes	914.82	922.49
Loglogistic	No	569	576.66	Yes	911.67	919.34
Lognormal	Yes	567.86	575.51	Yes	905.73	913.4
Gompertz	No	570.55	578.2	No	910.29	917.96
Generalised gamma	Yes	569.63	581.11	Yes	903.18	914.69

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DF, disease-free; LRR, locoregional recurrence. Parametric distribution in **bold** is applied in the base case analysis.

Figure 22 shows the KM curves presented alongside the extrapolated fits for osimertinib, which is displayed up to 8 years as patients in the osimertinib arm are assumed cured from 8 years in the base case and beyond this, the extrapolated curves are not used. Given the expectations of a plateau and functional cure, the Gompertz, Weibull and loglogistic distributions were considered too pessimistic and clinically implausible. Figure 23 shows the KM curves presented alongside the extrapolated fits for the active monitoring arm, which is displayed up to 5 years as patients in the

active monitoring arm are considered cured from 5 years in the base case and beyond this, the extrapolated curves are not used. All curves provide a similar fit at the 5-year time point, with the exception of Gompertz. A summary of whether the curves are considered clinically plausible is provided in Table 22. If the cure timepoint is shifted beyond 5 and 8 years, respectively, then the clinical plausibility of these extrapolations needs to be reassessed.

Figure 24 presents the smoothed hazard plots, showing the decreasing hazards over time for the active monitoring arm, and a low risk of recurrence in the first two years of osimertinib, followed by a slight increase afterwards, however, this is likely skewed due to the low number at risk. Figure 25 compares the smoothed trial hazards with the hazards predicted by the parametric models. For active monitoring, generalised gamma overpredicts the within-trial increase in hazards; for osimertinib, the generalised gamma overpredicts the downturn in hazards towards the end of the trial.

Given the AIC/BIC statistics, extrapolations, and hazards, lognormal was selected in the base case for both the osimertinib and active monitoring arms.

The clinical plausibility of the aggregated DFS curve (i.e., including TP1, TP2, TP3 and the cure assumptions) was validated with clinicians (detailed in Section B.3.3.8).

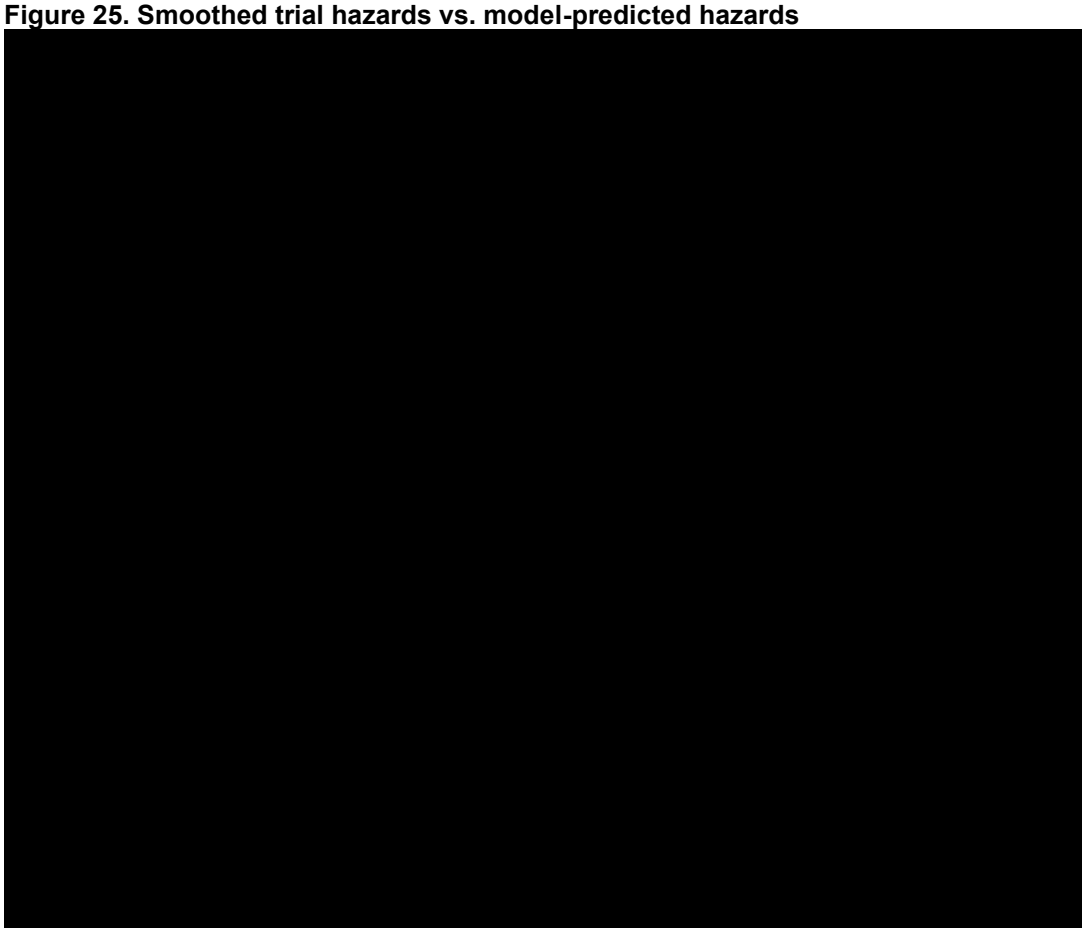
Figure 22. Extrapolations for DF to LRR (TP1) for osimertinib

Abbreviations: DF, disease-free; LRR, locoregional recurrence; TP1, transition probability 1.

Figure 23. Extrapolations for DF to LRR (TP1) for active monitoring

Figure 24. Smoothed hazard plots for DF to LRR (TP1)

Figure 25. Smoothed trial hazards vs. model-predicted hazards



B.3.3.3.3 TP2: Disease-free (DF) to 1st line treatment of distant metastasis (DM1)

KM data

For the model's DF to DM1 transition, KM data for the time to locoregional recurrence from the ADAURA trial was used (Figure 26). Parametric curves were fitted to the data, and the curve selection was based on the methods described below.

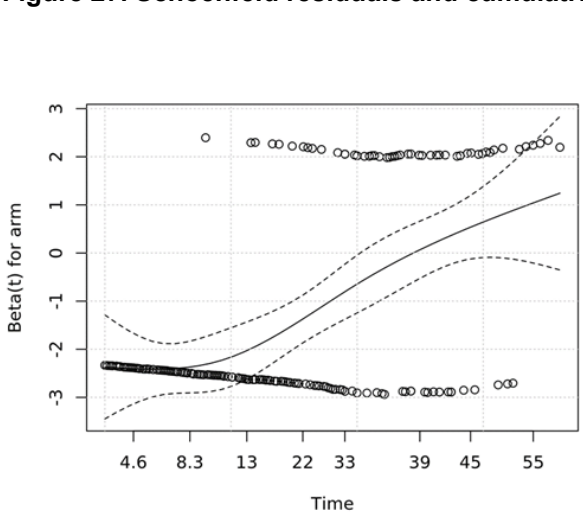
Figure 26. KM curves for time to distant metastases recurrence in the osimertinib and placebo (active monitoring) arms of ADAURA

Abbreviation: KM, Kaplan-Meier.

Assessment of the proportional hazards assumption

Figure 27 presents the cumulative hazards plot and the Schoenfeld residuals plot for the transition DF to DM1. The Schoenfeld residuals plot and the Schoenfeld residuals test ($p<0.001$) indicate that the proportional hazards assumption is violated. Therefore, only individual fits were considered in the model.

Figure 27. Schoenfeld residuals and cumulative hazard plot for the transition DF to DM1 (TP2)



[redacted]

Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DF, disease-free; LRR, locoregional recurrence.

Selection of base case parametric distributions

Parametric distributions fit separately to each trial arm were selected based on their goodness of fit statistics, visual inspection and consideration of whether the extrapolation was clinically plausible.

Table 23 presents the AIC and BIC statistics, which shows lognormal provides the best within-trial fit for osimertinib, although all distributions fall within 6 points of each other, with the exception of the Gompertz. For active monitoring, the lognormal and generalized gamma distributions provide the best within-trial fit, here the lognormal is chosen since this distribution aligns better with the expected cure after 5 years.

Table 23. AIC and BIC values for the fitted distributions to the transition DF to DM1

	Osimertinib			Placebo (active monitoring)		
Model	**Clinically viable**	**AIC**	**BIC**	**Clinically viable**	**AIC**	**BIC**
Exponential	No	632.37	643.84	Yes	1,361.67	1,365.51
Weibull	No	631.33	638.98	Yes	1,362.21	1,369.88
LOGLOGISTIC	Yes	636.02	643.67	Yes	1,354.22	1,361.90
Lognormal	Yes	630.35	638.01	Yes	1,344.13	1,351.80
Gompertz	No	675.46	679.29	Yes	1,353.08	1,360.76
Generalised gamma	Yes	630.62	638.27	Yes	1,335.814.13	1,347.32

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DF, disease-free; DM, distant metastasis. Parametric distribution in **bold** is applied in the base case analysis.

Figure 28 shows the KM curves presented alongside the extrapolated fits for osimertinib, which is displayed up to 8 years as the osimertinib arm is assumed cured from 8 years in the base case and beyond this, the extrapolated curves are not used. The exponential distribution was ruled out as it visually provided a poor fit to the data. Given the expectations of functional cure, the

Gompertz and Weibull distributions were considered clinically implausible. Figure 29 shows the KM curves presented alongside the extrapolated fits for the active monitoring arm, which is displayed up to 5 years as patients in the active monitoring arm are considered cured from 5 years in the base case and beyond this, the extrapolated curves are not used. All curves provide a similar fit at the 5-year time point. A summary of whether the curves are considered clinically plausible is provided in Table 23. If the cure timepoint is shifted beyond 5 and 8 years, respectively, then the clinical plausibility of these extrapolations needs to be reassessed.

Figure 30 presents the smoothed hazard plots, showing the decreasing followed by plateauing hazards over time for the active monitoring arm, and a low risk of recurrence in the first two years of osimertinib, followed by a slight increase afterwards, however, this is likely skewed due to the low number at risk. Figure 31 compares the smoothed trial hazards with the hazards predicted by the parametric models. For active monitoring, generalised gamma slightly overpredicts the within-trial increase in hazards in the first years; for osimertinib, the lognormal underpredicts the downturn in hazards towards the end of the trial, whereas the loglogistic distribution is more in line with the within-trial hazards.

The clinical plausibility of the aggregated DFS curves (i.e., including TP1, TP2, TP3 and the cure assumptions) were validated with clinicians (detailed in Section B.3.3.8). In addition, in the 2023 clinical interviews KEEs were asked to consider whether the lognormal/loglogistic distributions or generalised gamma/Gompertz distributions provided a better fit to the active monitoring arm for this transition (extrapolated up to 8 years). All clinicians found this extrapolation challenging to validate with three providing a response; two indicated loglogistic/lognormal and one indicated generalised gamma/Gompertz.

Given the AIC/BIC statistics, extrapolations, hazards, and clinical opinion lognormal was selected in the base case for the active monitoring arm, and loglogistic for the osimertinib arm.

Figure 28. Extrapolations for DF to DM1 (TP2) for osimertinib

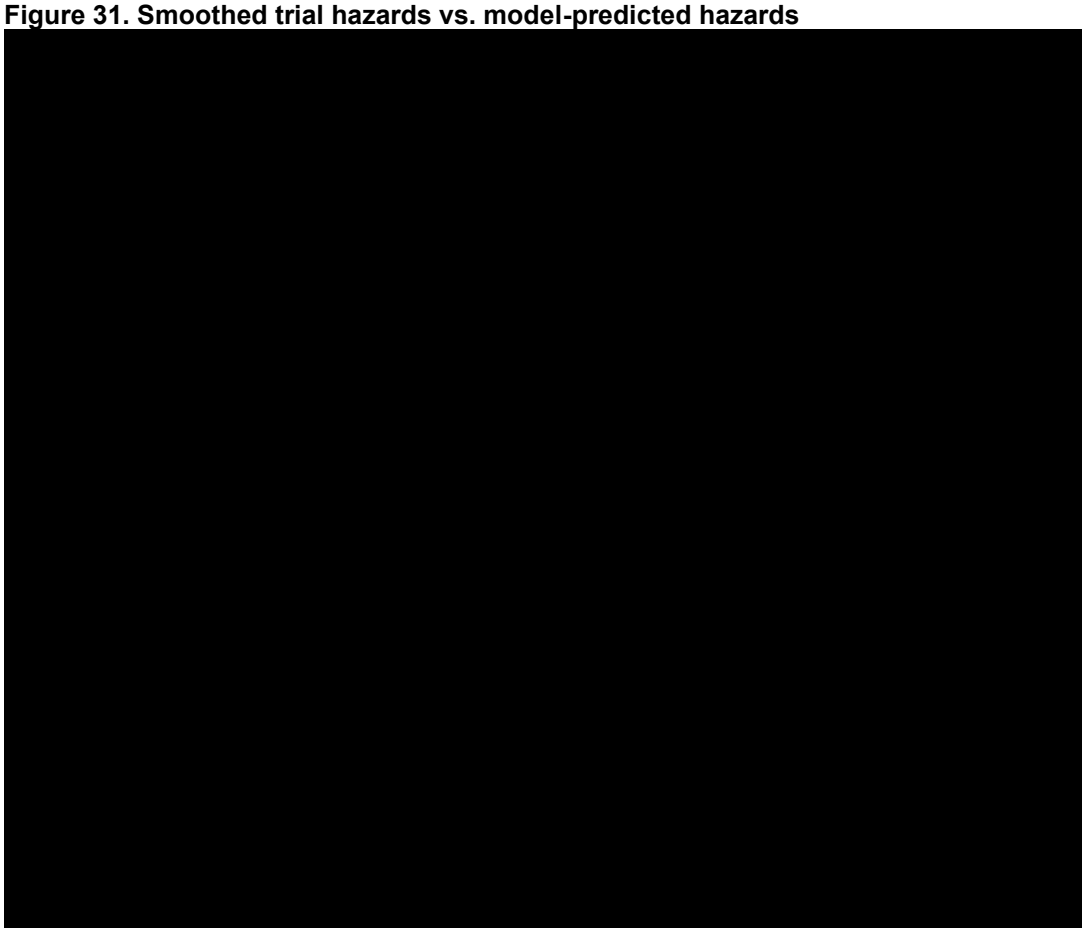
Abbreviations: DF, disease-free; DM, distant metastasis; TP2, transition probability 2.

Figure 29. Extrapolations for DF to DM1 (TP2) for active monitoring

Abbreviations: DF, disease-free; DM, distant metastasis; TP2, transition probability 2.

Figure 30. Smoothed hazard plots for DF to DM1 (TP2)

Figure 31. Smoothed trial hazards vs. model-predicted hazards



B.3.3.3.4 TP3: Disease-free (DF) to death

At the ADAURA April 2022 data cut-off, very few deaths had occurred among stage IB–IIIA patients who remained DF (one in the osimertinib arm and six in the placebo (active monitoring) arm).[3,89] As a result, no parametric models could be reliably fitted to the data to estimate the transition from DF state to death. This transition was therefore modelled using the background mortality in the age-adjusted UK population.[120]

B.3.3.4 *Post-DF calibration*

Transitions post-DFS are informed by CancerLinQ and FLAURA, as ADAURA data were too immature to be used directly in the model. Whilst data from FLAURA was considered the most appropriate (see Appendix M.1 for details) and clinically relevant data to inform the transitions in the distant metastatic states by all clinicians surveyed in the 2020 and 2023 interviews, the FLAURA population consists of stage IIIB/IV newly diagnosed metastatic patients which is distinctly different from ADAURA patients who have received radical treatment and progressed to metastatic disease.

To investigate whether the outcomes for patients with post-surgery recurrence compared to newly diagnosed stage IIIB/IV patients could be expected to differ, an SLR was conducted. This focused on studies in EGFRm NSCLC reporting either the median and/or HR for PFS and/or OS in both the post-surgery recurrence and newly diagnosed stage IIIB/IV setting. This SLR search resulted in 1,049 hits, of which eight remained after the full-text screening (Appendix T). All studies were in patients with EGFRm NSCLC receiving treatment in first line therapy for metastatic disease.[135-138] All identified studies were in Japanese patients only.

Patients with post-surgery recurrence consistently report better survival once diagnosed with metastatic disease compared with those with newly diagnosed stage IIIB/IV NSCLC. The efficacy improvement in median PFS and OS is relatively consistent (0.603 vs. 0.669), as is the efficacy improvement the HRs for PFS and OS (0.448 vs. 0.472), see Table 24. This suggests that patients who are post-surgery but have progressed to stage IIIB/IV disease experience improved PFS outcomes in this setting compared to patients who are newly diagnosed with stage IIIB/IV disease, and that this efficacy improvement continues after disease progression, hence the improved OS outcomes.

Table 24. Efficacy improvement as found in literature

	Number of studies	Efficacy improvement (ratio of newly diagnosed vs post-surgery)	Total n
Median PFS[135-138]	4	0.603	377
Median OS[136]	1	0.669	172
PFS HR[138]	1	0.448	202
OS HR[136]	1	0.472	213

These findings were confirmed in the 2023 clinician interviews. Most (4/5) clinicians said they would expect survival outcomes for ADAURA patients who progressed to metastatic disease to perform better than a newly diagnosed patient with stage IIIB/IV disease.

As it was not possible to adjust for population differences between ADAURA and FLAURA using population matching methods (e.g., propensity score matching, due to the limited availability of relevant data for the matching), other methods of adjustment were explored. It was also not appropriate to synthesise the results from the SLR to adjust for population differences in the model, given the small number of studies, which are in a Japanese population only. Instead, the ADAURA OS KM curve was compared to the model-predicted OS curves and the differences between the curves were minimised. Transitions informed by ADAURA (TP1-2) were not calibrated, as these are informed by ADAURA. Transitions informed by general population mortality (TP3, TP5, and TP7) were not calibrated as it would be inappropriate to reduce the risk of death below that of the general population. The calibration factor was applied to the remaining transitions (TP4, TP6, and TP8), which all influence the OS curve without impacting the well-predicted DFS curve, and are all considered to be limited by the same rationale equally across both arms in the model. The details of this approach are described in the subsequent sections.

B.3.3.4.1 Theoretical framework

In order to find the value that minimises the differences between the modelled OS and the KM, first the area-under-the-curves (AUC) are calculated for both arms of the OS KM and the modelled OS curves. For the latter, the AUC is calculated from time 0 to the latest time point available for each arm of the OS KMs.

Using that the maximum time of a KM is t* and that the difference in survival probability S(t) at each time step is given by $\Delta S(t) = S(t) - S(t-1)$, we can calculate the AUC for the KM using:

$$AUC_{KM} = \sum_{t=o}^{t=t^*} \Delta S(t)$$

A similar approach is used for the modelled OS, with the same time increments as available for the equivalent KM. Using the different AUCs, we can calculate the absolute difference between the KM and modelled OS survival for both arms:

$$\Delta AUC = |AUC_{Modelled} - AUC_{KM}|$$

The value which minimizes these differences to adjust for the differences in the populations is labelled a ‘calibration factor’ (CF). The CF is applied as a hazard ratio to TP4 (LR→DM1), TP6 (DM1 → DM2) and TP8 (DM2 → Death) for both arms. This means that a change in CF is a change in the modelled survival and thus a change in the ΔAUC. CF is then calculated by finding the CF that minimises the sum of the absolute difference in the AUC for osimertinib and active monitoring:

$$CF = arg\min_{CF} \Delta AUC_{OS\,osi} + \Delta AUC_{OS\,pbo}$$

B.3.3.4.2 Practical implementation

In order to calculate the CF, the model settings were adjusted to ensure the outcomes replicated the ADAURA trial as closely as possible. The optimisation was performed using Microsoft Excel's Solver add-in, where the survival probability S(t) for the KMs and modelled OS are taken from the model traces (after mid-cycle correction) and solving for the CF input.

A value of [redacted] was found to minimise the sum of the ΔAUC for both arms, leading to the modelled curves matching the KMs visually. The approach and resulting calibration factor were also discussed with three clinicians from Canada and one from the UK.[37] They agreed with the approach and the magnitude of the calibration factor. The calibration factor was further validated by five UK based clinicians in the 1:1 interviews held in 2023. All five UK clinicians interviewed agreed that that aggregated model OS curves which included the calibration factor were reasonable. A scenario was conducted where the calibration factor is not applied, see section B.3.8.3.

B.3.3.5 *Modelling from locoregional recurrence (LRR) (TP4 and TP5)*

Due to limited post-recurrence follow-up data available from the ADAURA trial at the April 2022 data cut-off, the transitions from local/regional recurrence (LRR) to 1st line treatment of distant metastasis (DM1) was modelled using CancerLinQ data (Appendix M.2). This is a real-world database, collecting electronic health record data from 1.4 million US cancer patients. A retrospective analysis of data from CancerLinQ was conducted and data from 1 January 2014 to 31 December 2018 were used. From this database, patients with EGFRm-positive NSCLC in stage IB–IIIA following tumour resection ('ADAURA-like' population) who had experienced locoregional recurrence were selected (n=97). For each patient, the time to distant metastases is determined, defined as time to metastatic disease when a metastases diagnosis was found or the date of first systemic treatment in the absence of metastatic identification. In the absence of available data from ADAURA at data cut-off, the transition probability from LRR to DM1 was assumed to be equivalent between the osimertinib and placebo (active monitoring) arms. The use of these data for the model was supported by UK clinical experts, who considered the patient population comparable with the ADAURA patient population and generalisable to UK practice (table with baseline characteristics of patients from CancerLinQ is presented in Appendix M.2.2).[46]

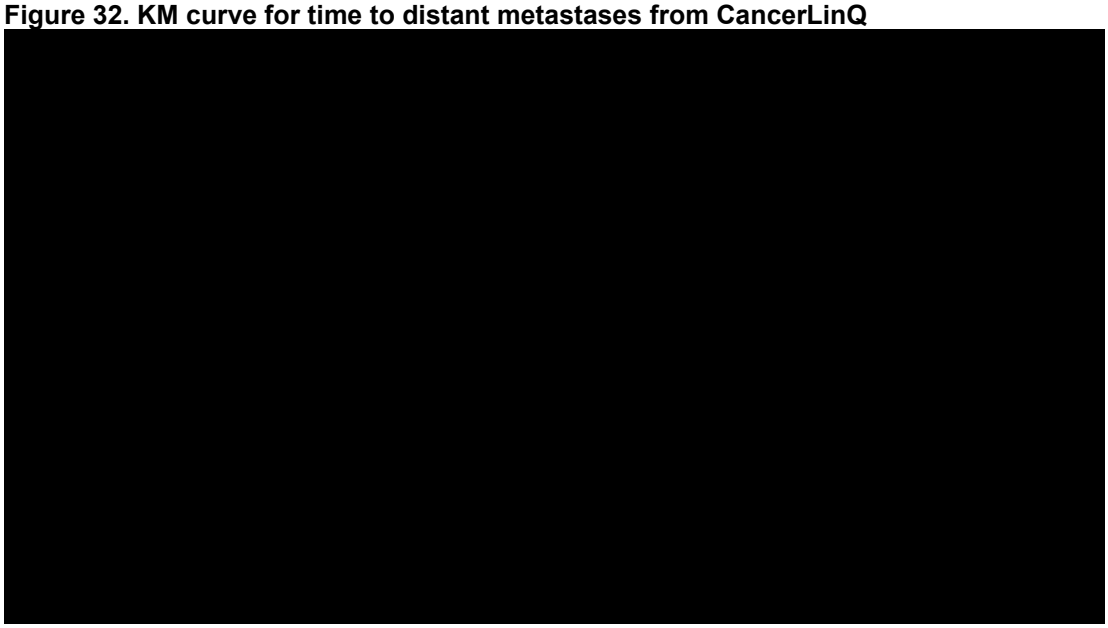
The CF was applied to the CancerLinQ TPs to align with the ADAURA 2023 OS data cut, as described in section B.3.3.4.

B.3.3.5.1 TP4: LRR to 1st line treatment of distant metastasis (DM1)

KM data

For the transition from LRR to DM1, KM data for the time to distant metastases from the CancerLinQ database was used. Parametric curves were fitted to the data presented in Figure 32 , and selection was based on the methods described below.

Figure 32. KM curve for time to distant metastases from CancerLinQ



Abbreviation: KM, Kaplan-Meier.

Assessment of the proportional hazards assumption

Since the data were analysed as one group, no proportional hazards assumption testing was required.

Selection of base case parametric distributions

Individual parametric models were assessed for their goodness of fit based upon visual inspection and AIC/BIC statistics, and the clinical plausibility of the extrapolation was considered. Figure 33 shows the fits and extrapolations for the transition from LRR to DM1 (TP4), with the AIC and BIC values presented in Table 25.

Patients who transition to LRR can receive radical therapy and have another opportunity to be functionally cured. The cure assumption is not explicitly modelled in the LRR state on the basis of clinical opinion (see Section B.3.3.3.1). Given this, distributions that were overly pessimistic were considered clinically implausible, and the exponential and Weibull curves were excluded.

Similarly, the Gompertz and generalised gamma distributions were excluded because of their overly optimistic long-term estimates. The log-normal and log-logistic distributions appear similar based upon visual inspection, however AIC and BIC values indicate the log-normal distribution is preferred based on best statistical fit (Table 25).

Table 25. AIC and BIC values for the fitted distributions to the transition LRR to DM1

Model	Clinically viable	AIC	BIC
Generalised gamma	No	422.30	430.03
Lognormal	Yes	427.52	432.67
Loglogistic	Yes	431.48	436.63
Gompertz	No	432.72	437.87
Weibull	No	436.34	441.49

Exponential	No	447.83	450.40

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DM1, 1st line distant metastasis; LRR, locoregional recurrence. Parametric distribution in **bold** is applied in the base case analysis.

Figure 33. Extrapolation of LRR to DM1 (TP4)

Abbreviations: DM1, 1st line distant metastasis; LRR, locoregional recurrence; TP4, transition probability 4.

B.3.3.5.2 TP5: LRR to death

In the CancerLinQ dataset only two death events were recorded, which is insufficient to fit a distribution on for extrapolation; therefore, due to the unavailability of other datasets for patients in the LRR state, and that patients in the LRR state are expected to experience a degree of disease recurrence prior to death. Therefore, this population, this transition was modelled using background mortality from the age-adjusted UK population.[120] It should be noted that patients in the LRR state are still at higher risk of death than patients in the DF state because of the higher likelihood of developing distant recurrence and the higher associated mortality risk associated with distant metastases.

B.3.3.6 *Modelling of distant metastases (TP6 to TP8)*

For both treatment arms, the transition probabilities from DM1 and DM2 were calculated based on the distribution of first-line and second-line treatments for advanced EGFRm NSCLC. The primary data source used to model the survival of patients with metastatic EGFRm-positive NSCLC was the FLAURA trial, as described in section B.3.3.1. Since the FLAURA study used PFS, time to subsequent therapy and OS as endpoints, the datasets required for the extrapolation of each transition probability cannot be derived directly. Therefore, the competing risks methodology described by Williams et al, 2017,[127] was used to determine each dataset for use in the model. In addition, instead of PFS, time to discontinuation of treatment was used due to the improved maturity of the data from the latest data cut-off from FLAURA (DCO2; June 2019), and also to be consistent with measurement of treatment costs in the DF state (based on time to treatment discontinuation).

As described in Section B.3.3.4, a CF was applied to the distant metastases transition probabilities for both osimertinib and active monitoring patients to adjust for population differences between previously untreated metastatic newly diagnosed metastatic and post-surgery patients.

Following input from UK clinical experts,[37,46] in the base case analysis it is assumed that retreatment with osimertinib in the DM1 state would be possible (Figure 16). However, the proportion of patients who would receive retreatment with osimertinib is uncertain as this is a step change in clinical practice and there have been no clinical studies in the use of osimertinib in patients who have received prior osimertinib treatment in the adjuvant setting. Due to the international setting of ADAURA, with different reimbursement policies for the involved countries, using the ADAURA trial to inform the percentage of retreatment in the model is not feasible. Therefore, it is implausible to assume that all patients would receive retreatment with osimertinib on progression to DM1. In addition, clinical experts advised that retreatment with other TKIs (including first and second-generation EGFR-TKIs) would not be considered as these are generally considered to be less potent and less efficacious versus osimertinib. Whilst the proportion of patients is uncertain, the six UK clinicians in the 2020 survey advised that retreatment with osimertinib would at least be considered in practice if (i) patients did not discontinue their adjuvant therapy within 36 months of treatment initiation and (ii) did not experience disease recurrence (LRR or distant metastasis) within 48 months.[46] The UK clinicians in the 2023 interviews advised that retreatment with osimertinib would be considered in practice if patients had completed three years of treatment and then progressed, or if they discontinued due to adverse events (i.e., did not discontinue due to progression whilst on osimertinib). Some clinicians in the 2023 interviews indicated that they may consider retreatment earlier than 12 months post-discontinuation, however

none of the clinicians interviewed had experience with requiring to consider retreatment in practice (i.e., patients hadn't completed 3 years of treatment and progressed). In the model base case retreatment with osimertinib is assumed to occur after a minimum of four years from treatment initiation. Scenario analyses are also provided exploring the impact of retreatment at 3.5 (3 years of treatment plus 6 month break) and 5 years in the model. Also, as noted above given the uncertainty in the proportion of patients retreated with osimertinib, the economic model assumes that 50% of patients would be retreated at the five–year time point, and alternative proportions are also explored in scenario analyses.

For the remaining 50% of patients who are not retreated with osimertinib after the five-year timepoint or those who progressed before the four-year timepoint it was assumed they would be treated with platinum doublet chemotherapy. However, as the standard of care in FLAURA was first-generation TKI (erlotinib/gefitinib), the efficacy of chemotherapy could be expected to be overestimated in the model by applying transition probabilities reflective of a more efficacious therapy than chemotherapy in the DM state. A network meta-analysis by Holleman et al was identified which included studies of standard of care TKIs in advanced EGFRm NSCLC. This estimated a PFS HR of 2.325 comparing chemotherapy to gefitinib, which was applied in the model base case to the transition from DM1 to DM2 (TP6).[139]

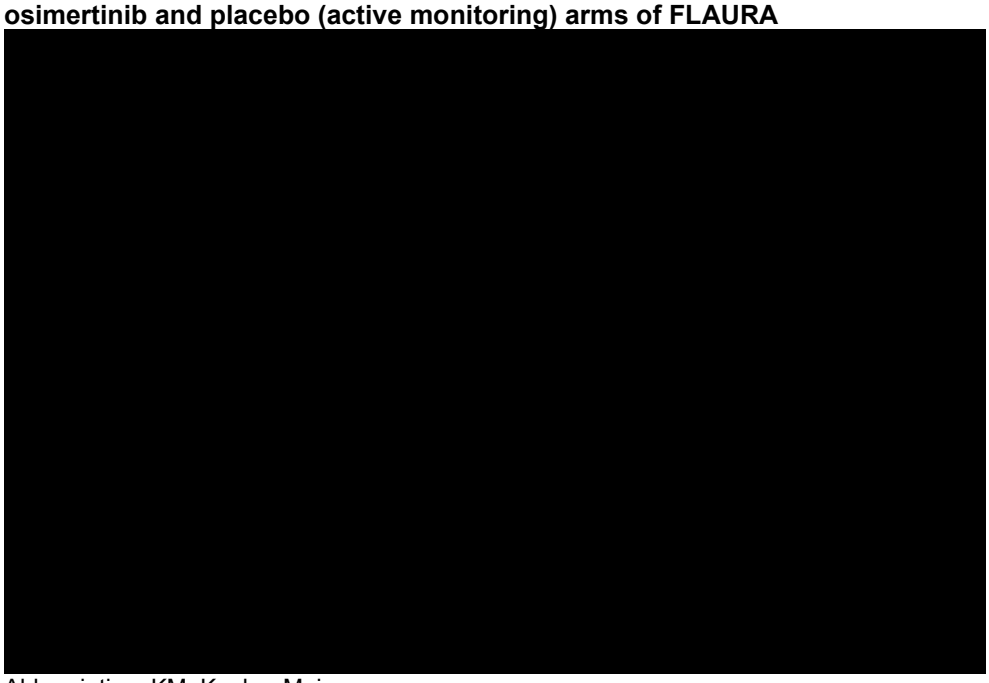
Finally, it is assumed that most patients who received placebo (active monitoring) in DF will be treated with osimertinib at DM1. As osimertinib is the most potent and efficacious TKI compared to older TKIs as demonstrated by the FLAURA trial and confirmed by clinicians, it is assumed that it would be a preferred treatment over other treatments for these patients. Acquired market share data suggests that 83% receive osimertinib, and 9% / 5% / 3% for afatinib / erlotinib / gefitinib, respectively.[78]

B.3.3.6.1 TP6: 1st line treatment of distant metastasis (DM1) to 2nd+ line treatment of distant metastasis (DM2)

KM data

For the model's DM1 to DM2 transition, KM data for the time to discontinuation of treatment (TTD) (censoring deaths) from the FLAURA trial were used instead of PFS data as RECIST PFS data were only collected until DCO1 (June 2017) in the FLAURA trial. Conversely TTD and OS data were collected until DCO2 (June 2019) when 60% OS event maturity was reached. Parametric curves were fitted to the data presented in Figure 34, and curve selection was based on the methods described below.

Figure 34. KM curves for the time to discontinuation of treatment (censoring deaths) in the osimertinib and placebo (active monitoring) arms of FLAURA

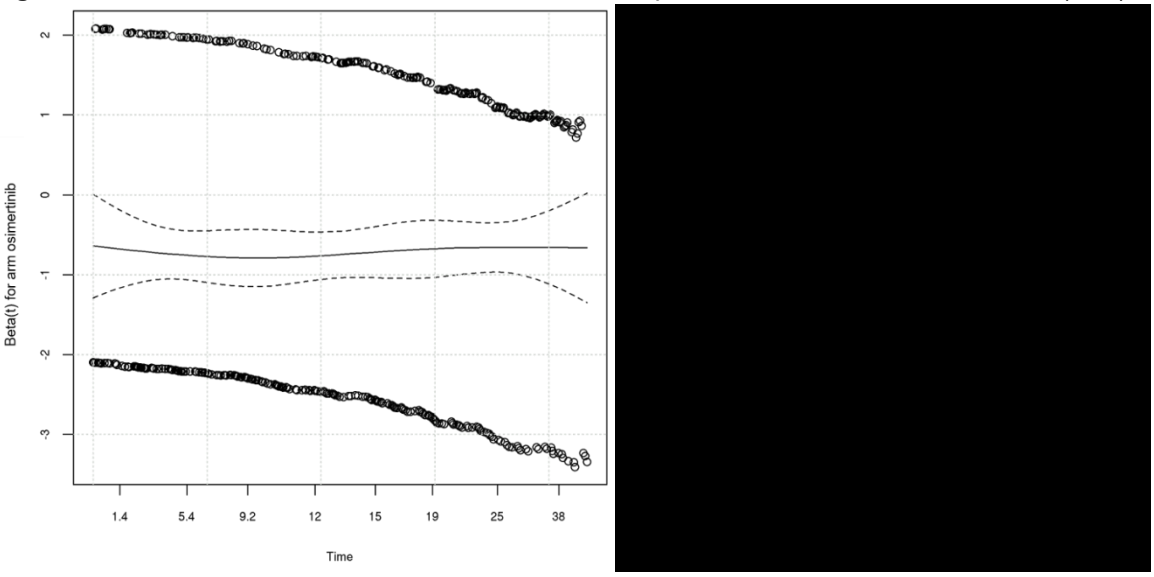


Abbreviation: KM, Kaplan-Meier.

Assessment of the proportional hazards assumption

The Schoenfeld residuals and cumulative hazard plot for the transition DM1 to DM2 is shown in Figure 35, with the statistical test results provided in Table 26. Since both the cumulative hazard plot and the Schoenfeld residuals plot show a linear trend, the PH assumption was assumed to hold (p=0.777). Therefore, both combined fits (where the same distribution is fitted to both arms, with a treatment effect on the active arm), and individual fits (where each arm is fitted to a separate distribution) can be used; however due to maturity of the data, independent fits were preferred.

Figure 35. Schoenfeld residuals and cumulative hazard plot for the transition DM1 to DM2 (TP6)



Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; TP6, transition probability 6.

Selection of base case parametric distributions

Individual parametric models were assessed for their goodness of fit based upon visual inspection and AIC/BIC statistics, and the clinical plausibility of the extrapolation was assessed . Figure 36 and Figure 37 show the fits and extrapolations for the transition from DM1 to DM2 (TP6), with the AIC and BIC values presented in Table 26. Based on visual inspection, the loglogistic and lognormal distributions were deemed to overfit the tail in both arms from the FLAURA trial, and led to predictions of almost 10% still alive after 10 years, and were thus considered clinically implausible and were excluded. Of the four remaining clinically-plausible distributions resulting in very similar shape of the curves and estimates, the Weibull was selected for the base case analysis as it shows the best statistical fit based on the AIC and BIC values (Table 26) in both arms.

Table 26. Goodness of fit for DM1 to DM2

		Osimertinib			SoC (erlotinib/gefitinib)	
Model	**Clinically viable**	**AIC**	**BIC**	**Clinically viable**	**AIC**	**BIC**
Weibull	Yes	1865.18	1872.45	Yes	1945.91	1953.15
Generalised gamma	Yes	1866.59	1877.48	Yes	1947.90	1958.77
Gompertz	Yes	1868.25	1875.51	Yes	1950.20	1957.45
Exponential	Yes	1867.24	1870.87	Yes	1951.26	1954.89
Loglogistic	No	1865.74	1873.00	No	1966.60	1973.85
Lognormal	No	1886.11	1893.37	No	1999.94	2007.19

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; SoC, standard of care. Parametric distribution in **bold** is applied in the base case analysis.

Figure 36. Extrapolation of DM1 to DM2 (TP6) – FLAURA's osimertinib arm

Abbreviations: DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; TP6, transition probability 6.

Figure 37. Extrapolation of DM1 to DM2 (TP6) – Flaura's SoC (erlotinib / gefitinib) arm

Abbreviations: DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; TP6, transition probability 6.

B.3.3.6.2 TP7: 1st line treatment of distant metastasis (DM1) to death

KM data

For the model's DM1 to death transition, pooled KM data (combined data from both treatment arms) for the time to death (censoring discontinuation of treatment) from the FLAURA trial was used given the low number of death events observed across treatment arms (n=11) and as the stratified analysis showed no difference between treatment groups. Parametric curves were fitted to the data presented in Figure 38 and the base case was selected applying the methods described below.

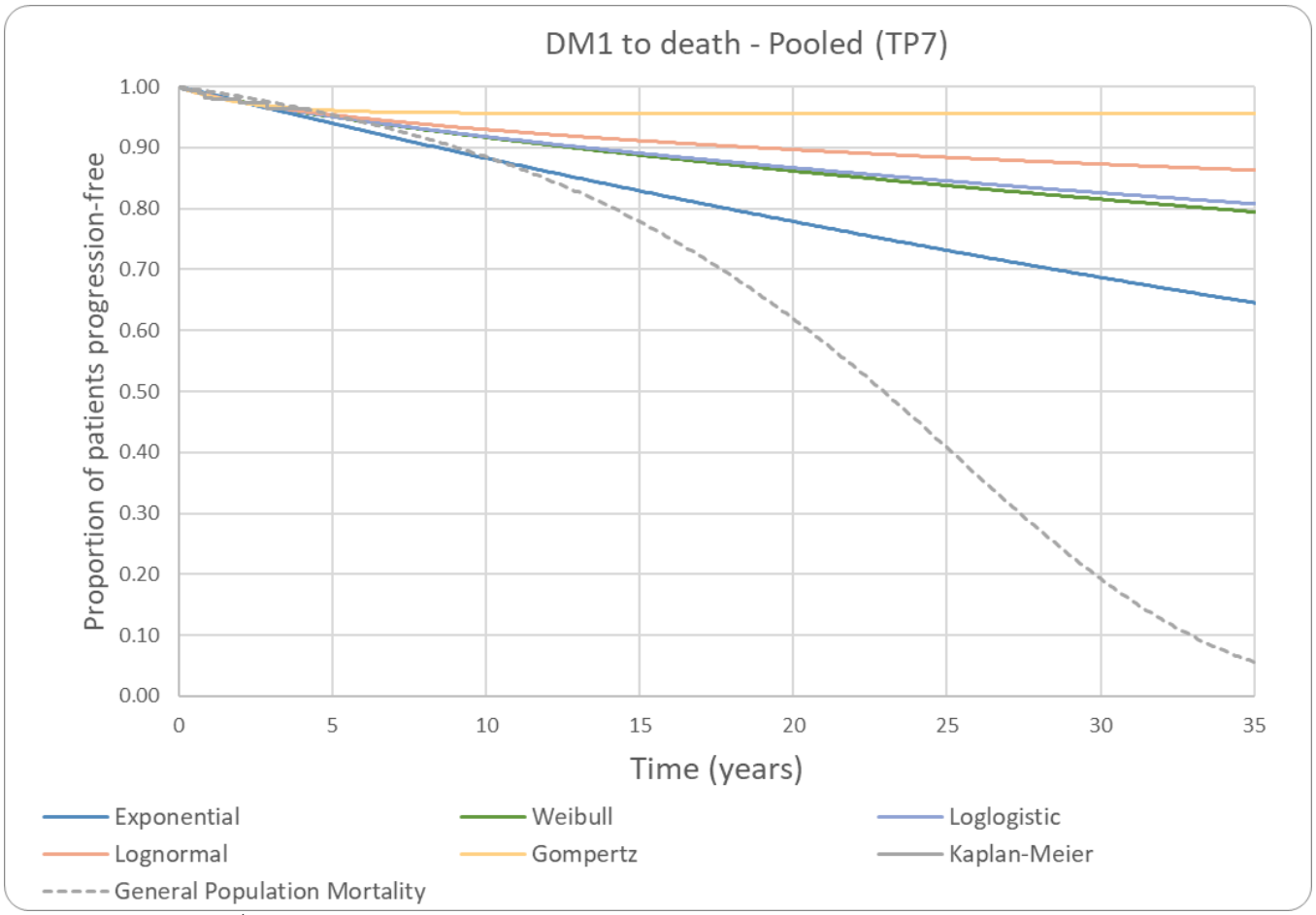
Figure 38. KM curves for the time to death (censoring discontinuation of treatment) using pooled data of both treatment arms of FLAURA

Abbreviation: KM, Kaplan-Meier.

Selection of base case parametric distributions

Parametric distributions were selected based on their goodness of fit and whether the extrapolation is clinically realistic. Although the distributions as shown in Figure 39 fits the KM data from FLAURA well, overall, the extrapolations are not clinically plausible as they generally provide higher survival estimates than the application of background mortality rates, whereas the generalized gamma did not converge. However, the exponential distribution has the most clinically plausible downward trend for patients in a metastatic setting and best statistical fit based on AIC and BIC values (Table 27); therefore, this distribution was applied until the hazard of the background mortality exceeds it. Thereafter, background mortality based on the age-adjusted UK population was applied. This is considered to be a conservative assumption, given more patients in the active monitoring arm progress to the DM1 state compared to the osimertinib arm.

Figure 39. Extrapolation of DM1 to death (TP7)



Abbreviations: DM1, 1st line distant metastasis; TP7, transition probability 7.

Table 27. Goodness of fit for DM1 to death

		Pooled	
Model	**Clinically viable**	**AIC**	**BIC**
Weibull	No	175.94	184.58
Generalised gamma	No	N/A	N/A
Gompertz	No	175.4	184.05
Exponential	Partial	174.97	179.29
Loglogistic	No	175.91	184.55
Lognormal	No	175.38	184.03

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DM1, 1st line distant metastasis. Parametric distribution in **bold** is applied in the base case analysis.
The generalized gamma distribution did not converge

B.3.3.6.3 TP8: 2nd line treatment of distant metastasis (DM2) to death

KM data

For the model's DM2 to death transition, the time from treatment discontinuation to death data from the FLAURA trial were used. Data from the patients randomised to osimertinib in FLAURA were applied to patients occupying the DM2 state in the active monitoring arm and vice versa. Parametric curves were fitted to the separate treatment arms as presented in Figure 40, applying the methods described below. The calibration factor was applied to the parametric curves.

As per the NICE (2020) Lung Cancer Algorithm for non-squamous NSCLC, patients requiring chemotherapy for advanced or metastatic disease, after treatment with osimertinib or other EGFR-TKIs, are eligible for the treatment regimen of atezolizumab plus bevacizumab, carboplatin and paclitaxel (IMPower150 regimen). Based on the clinical expert opinion and market share data for the UK, the expected usage of this treatment regimen following targeted therapy for metastatic EGFRm NSCLC is limited. Therefore, [redacted] of patients in the base case model would be eligible for the IMPower150 regimen.[78] The efficacy is modelled using the ABCP-arm of the EGFR-mutated subpopulation of the IMPower150 trial, i.e. patients with an EGFR mutation who had experienced disease progression with previous TKI therapy.[122] For this, OS data from the IMPower150 study[122] were digitised and pseudo-patient level data were derived using the algorithm developed by Guyot et al 2012.[133] Survival models were fit using the same process as outlined in Section B.3.3.1.1. The Weibull distribution was selected for consistency with the FLAURA selection, which is detailed below. Then, a weighted survival extrapolation is calculated based on 80% FLAURA post-TDT efficacy and [redacted] via IMPower150.

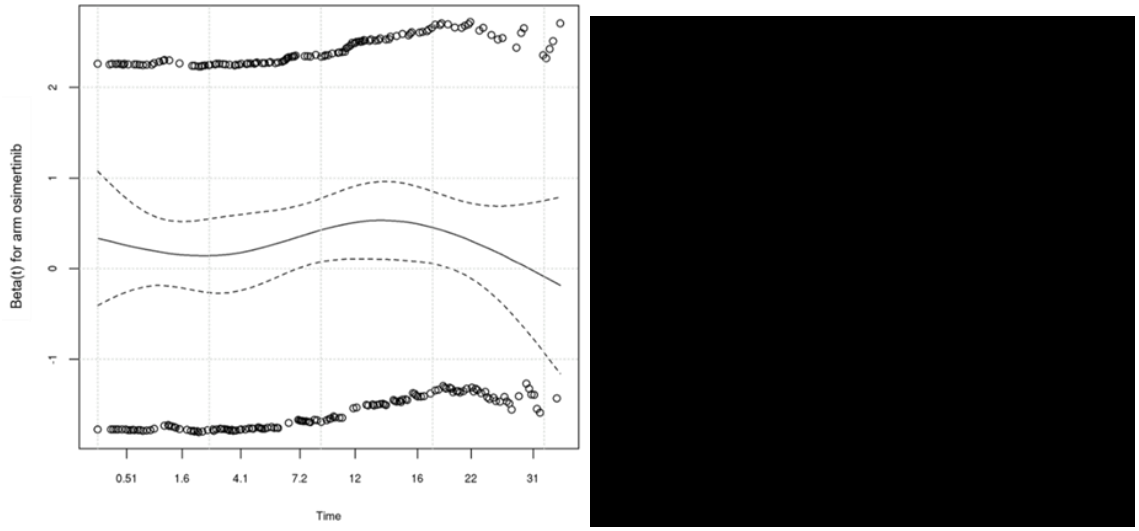
Figure 40. KM curves for post time to discontinuation of treatment in the osimertinib and SoC arms of FLAURA

Abbreviations: KM, Kaplan-Meier; SoC, standard of care.

Assessment of the proportional hazards assumption

The Schoenfeld residuals and cumulative hazard plot for the transition DM2 to death is shown in Figure 41. Since the Schoenfeld residuals and cumulative hazard plot shows a linear trend, we can assume the proportional hazards assumption does hold (p-value of 0.812). Since the proportional hazards assumption holds, combined fits where the same distribution is fitted on both arms with a treatment effect on the active arm, as well as individual fits where each arm is fitted individually, can be used. However due to maturity of the data, independent fits were preferred.

Figure 41. Schoenfeld residuals and cumulative hazard plot for the transition DM2 to death (TP8)



Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DM2, 2nd line distant metastasis; TP8, transition probability 8.

Selection of base case parametric distributions

FLAURA

Individual parametric models were assessed for their goodness of fit based upon visual inspection and AIC/BIC statistics, and the clinical plausibility of the extrapolation was considered. Figure 42 shows the fits and extrapolations for the transition from DM2 to death (TP8), with the AIC and BIC values provided in Table 28. The Gompertz provided implausibly long tails in the survival curves for both arms, whilst the log-logistic and log-normal provided poor fits to the data. Based on statistical fit, the Weibull distribution provides the best fit; therefore, this distribution was selected for the base-case analysis in both arms.

Table 28. Goodness of fit for DM2 to death

		Osimertinib			SoC (erlotinib/gefitinib)	
Model	**Clinically viable**	**AIC**	**BIC**	**Clinically viable**	**AIC**	**BIC**
Weibull	Yes	1106.90	1113.55	Yes	1316.81	1323.93
Generalised gamma	Yes	1108.51	1118.48	Yes	1318.73	1329.40
Loglogistic	No	1117.82	1124.47	No	1322.66	1329.78
Gompertz	No	1114.31	1120.96	No	1323.71	1330.83
Lognormal	No	1125.08	1131.72	No	1324.37	1331.48
Exponential	No	1118.40	1121.73	No	1329.18	1332.73

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DM2, 2nd line distant metastasis; SoC, standard of care; TP8, transition probability 8. Parametric distribution in **bold** is applied in the base case analysis.

Figure 42. Extrapolation of DM2 to death – FLAURA post-TDT osimertinib (TP8)

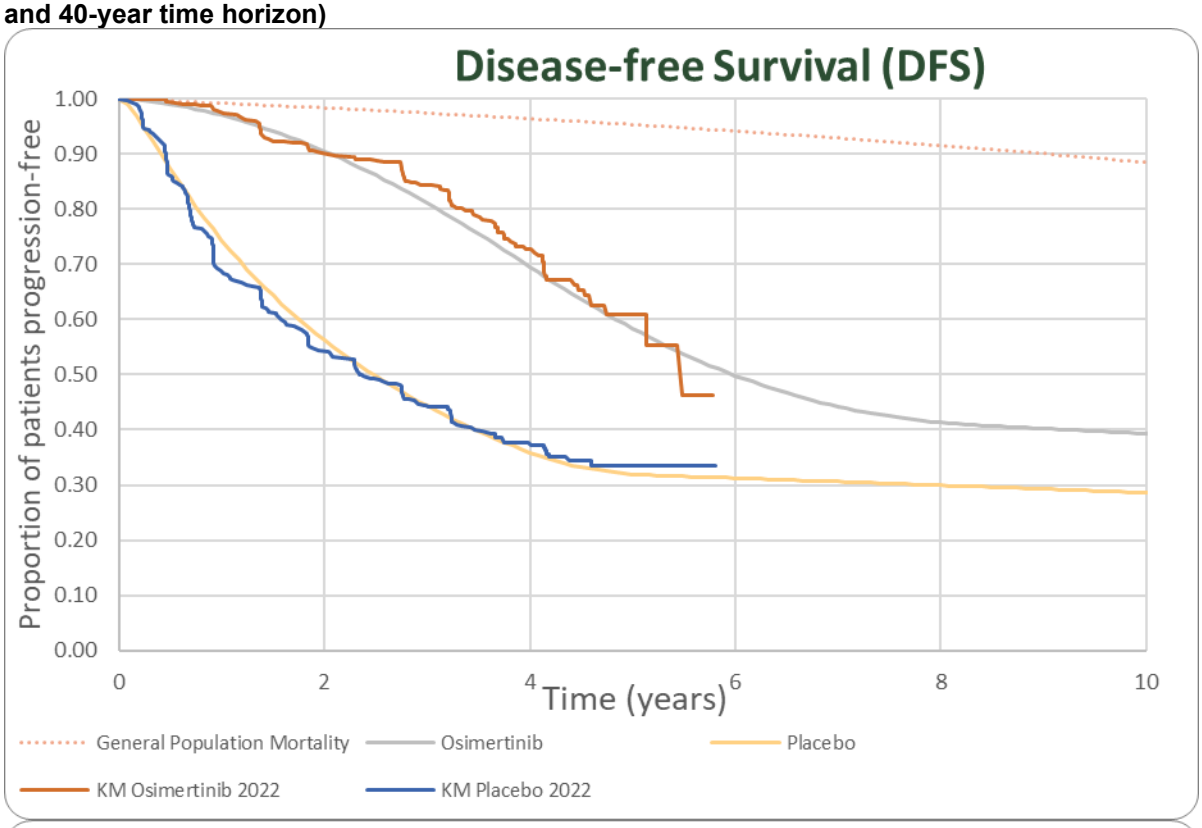
Abbreviations: DM2, 2nd line distant metastasis; TDT, time to discontinuation of treatment; TP8, transition probability 8.

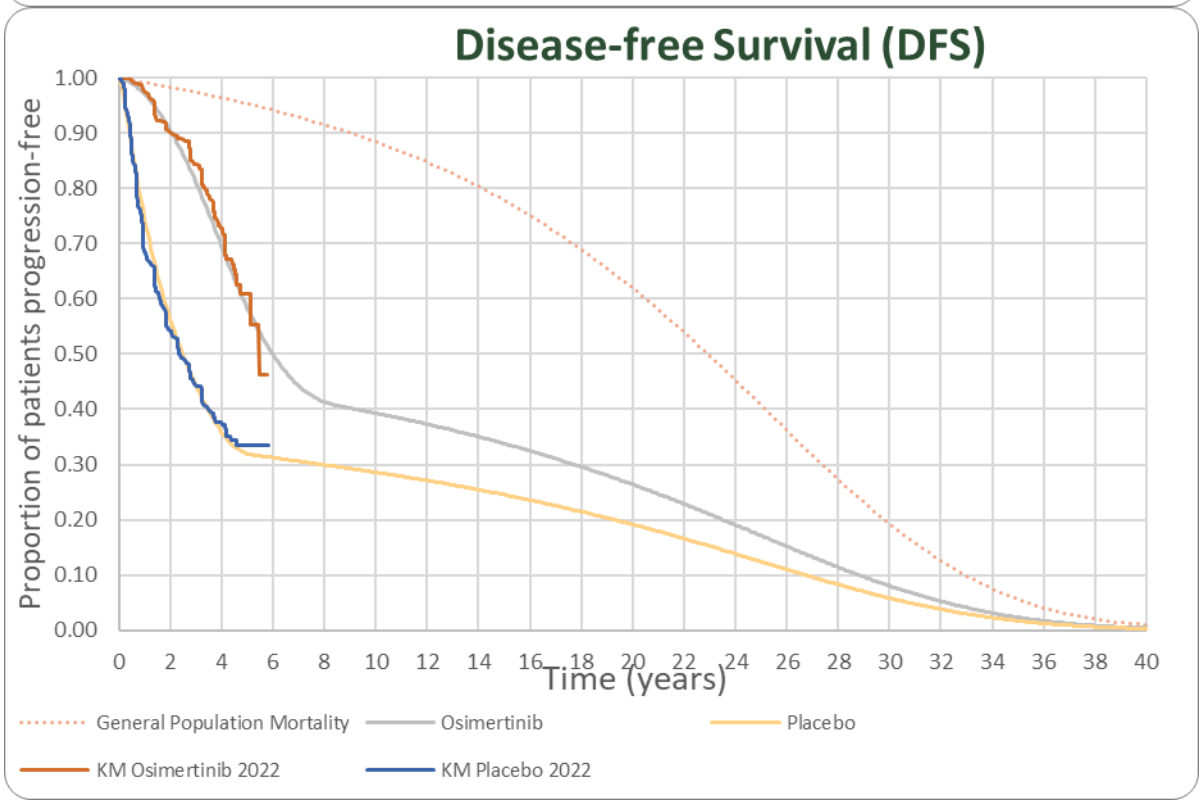
Abbreviations: DM2, 2nd line distant metastasis; TDT, Time to discontinuation of treatment; TP8, transition probability 8.

B.3.3.7 *Aggregated DFS and OS*

Reproducing the original endpoints of the modelled trial (ADAURA) is a key validation step for a Markov model. The base case is decided using the parametric distributions with the best statistical fit and clinical plausibility for each transition, with the calibration factor applied to TP4/TP6 /TP8, see B.3.3.4. This combination of distributions results in the aggregated DFS and OS shown in Figure 43 and Figure 44 respectively. In addition, scenario analyses were also performed to test different curve selections.

Figure 43. Aggregated DFS with cure assumption applied compared with ADAURA DFS (10 and 40-year time horizon)





Abbreviations: OS, overall survival

Table 29. Parametric distributions and data sources used for the base case transitions

Transition	Parametric distributions		Data source
TP1: DF → LRR	Osi: Lognormal	Active monitoring: Lognormal	ADAURA[27]
TP2: DF → DM1	Osi: Loglogistic	Active monitoring: Lognormal	ADAURA[27]
TP3: DF → Death	Background mortality		UK life tables[120]
TP4: LRR → DM1*	Lognormal		CancerLinQ[121]
TP5: LRR → Death	Background mortality		UK life tables[120]
TP6: DM1 → DM2*	Weibull		FLAURA[100]
TP7: DM1 → Death	Exponential / background mortality		FLAURA[100,120]
TP8: DM2 → Death*	Weibull		FLAURA[100]

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, locoregional recurrence.
*Calibration factor applied as described in section B.3.3.4

The aggregated DFS data for the placebo (active monitoring) arm is consistent with real-world clinical data derived from a cohort of patients with early-stage, resected EGFRm-positive NSCLC in England.[140] A total of 24 patients were identified that had undergone complete surgical resection with negative margins. Sixteen patients were female (66.6%) and 8 were male (33%) which is comparable with the gender distribution in ADAURA and applied in the economic model. A total of five patients were receiving adjuvant chemotherapy following surgery. The overall DFS rate at two years was 54%, which is consistent with DFS reported in the ADAURA KM and the extrapolated DFS applied in the cost-effectiveness model. It can therefore be assumed that initial active monitoring DFS estimates are representative of current clinical practice.

A landmark comparison for the base case is presented in Table 30 and Table 31. Comparing the model estimated DFS curves (Figure 44) with long-term published data, such as from the ANITA trial,[132] with the application of cure assumption (95% cured after 5 years), the DFS estimates for placebo (active monitoring) in ADAURA and the DFS KM data for active monitoring from ANITA are comparable as described in Section B.3.3.3.1. In terms of OS, at around eight years of follow up, the ANITA trial's placebo arm reached ~35–40% OS rate (based on Figure 2 from Douillard et al, 2006 [ANITA study]), which is also comparable to the model estimated OS results (after the application of the cure assumption and the calibration factor; B.3.3.4) at those points in time.

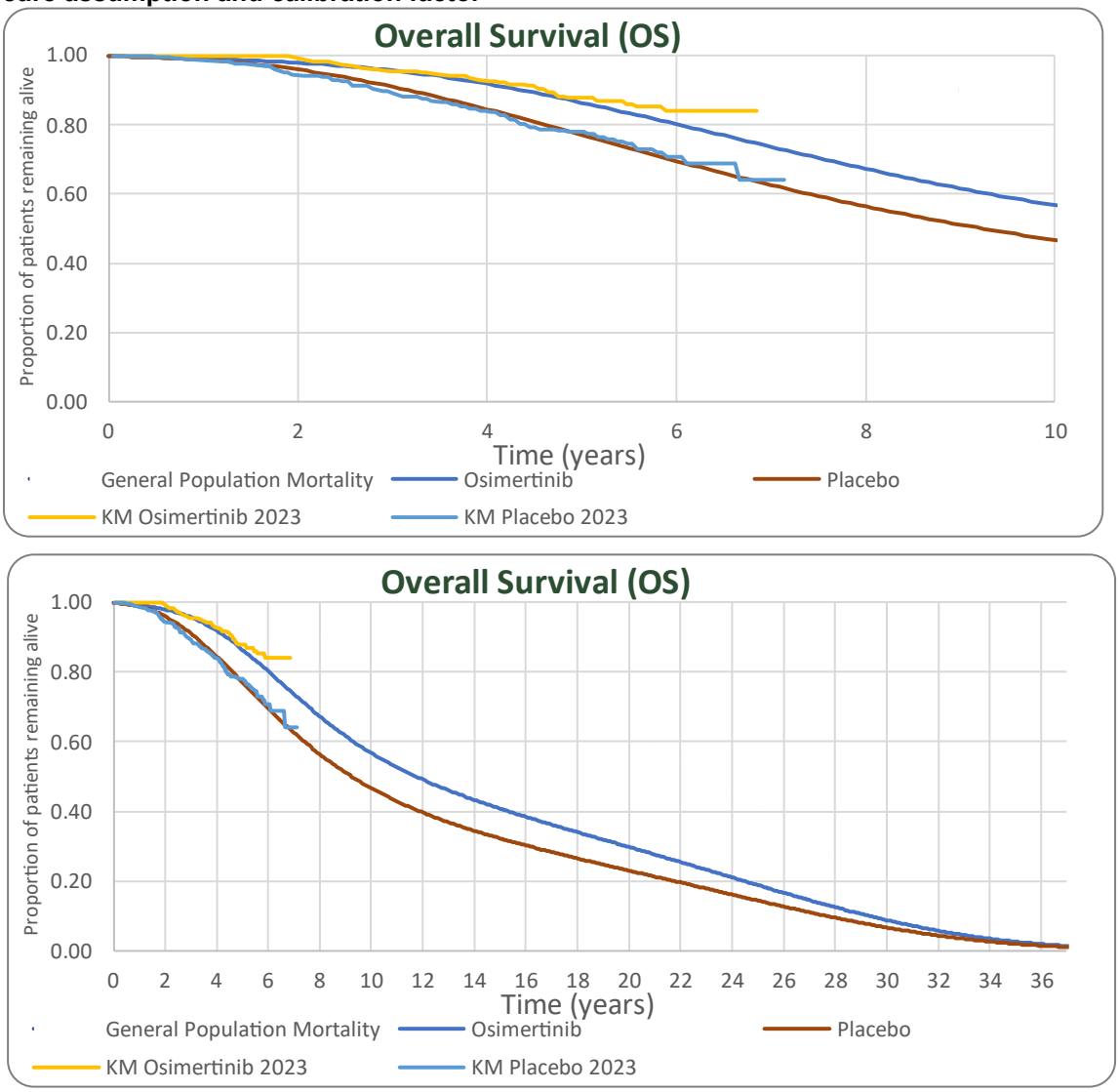
Table 30. Landmark comparison of aggregated DFS and ADAURA DFS (with cure assumption of 95% cured after 5 years for active monitoring and 8 years for osimertinib)

	Osimertinib - model	Osimertinib - ADAURA	Placebo (active monitoring) - model	Placebo - ADAURA
Median DFS (months)	72.0	65.2	18.0	28.1
% at 1 year	96.8	97.8	73.6	68.9
% at 2 years	90.2	90.1	55.7	54.5

	Osimertinib - model	Osimertinib - ADAURA	Placebo (active monitoring) - model	Placebo - ADAURA
% at 3 years	80.7	84.4	43.9	44.0
% at 4 years	69.0	72.7	35.6	37.7
% at 5 years	58.0	60.9	31.9	33.6
% at 10 years	39.3	-	28.6	-

Abbreviations: DFS, disease-free survival; NR, not reached.

Figure 44. Aggregated OS curve based on the fitted Kaplan-Meier data from ADAURA, applied cure assumption and calibration factor



Modelled aggregated OS of the ADAURA trial, with and without calibration factor.
Abbreviations: OS, overall survival

Table 31. Landmark comparison of aggregated OS and ADAURA OS (with cure assumption of 95% cured starting at 4 years)

	Osimertinib - model	Osimertinib - ADAURA	Placebo (active monitoring) - model	Placebo - ADAURA
Median OS (months)	146.0	-	115.0	-
% at 1 year	99.2	100.0	98.9	99.1
% at 2 years	98.0	99.6	96.1	94.6
% at 3 years	95.8	95.6	91.3	89.1
% at 4 years	92.0	93.1	85.0	84.2
% at 5 years	86.7	87.9	77.9	77.9
% at 10 years	58.5	-	50.3	-

Abbreviations: NR, not reached; OS, overall survival.
*Due to censoring/low number of patients at risk, and thus it is not representative of expected median OS

B.3.3.8 *Clinical expert assessment of applicability of clinical parameters and the calibration factor*

When the aggregated DFS and OS curves, incorporating the cure assumptions and CF, were presented to UK clinicians in the 2023 interviews, clinicians agreed that the within trial fit and extrapolations were clinically plausible.[37] For the DFS curves, it was considered plausible that a treatment benefit for adjuvant osimertinib treated patients compared with active monitoring treated patients would be sustained over time. Clinicians commented that some benefit gained from treatment would be expected to be maintained over time, as is modelled.[37]

B.3.4 *Measurement and valuation of health effects*

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

HRQoL was assessed in the ADAURA trial using the SF-36 questionnaire (version 2, standard) for the DF and LRR health states for both arms. The SF-36 consists of eight subscales measuring different domains: physical functioning, social role functioning, physical role functioning, bodily pain, general mental health, emotional role functioning, vitality (energy and fatigue), and general health perceptions.[141] The primary outcome measures of interest were time to deterioration of the two aggregated summary scores (MCS and PCS).

Assessments were made at the following time points: baseline, Day 1 (pre-dose), at 12 weeks, 24 weeks and then every additional 24 weeks from randomisation (±7 days) until treatment completion (3 years) or discontinuation.

In the FLAURA trial, assessing osimertinib as first-line treatment for patients with previously untreated, EGFR mutation–positive advanced NSCLC, HRQoL was assessed using the EORTC QLQ-C30 questionnaire. The assessed HRQoL data for progression-free patients aligns with the DM1 health state in the current economic model.

B.3.4.2 *Mapping and repeated measures analyses*

SF-36 data from both arms of the ADAURA trial were the primary source of health state utility values (HSUVs) in DF and LRR. The EQ-5D-3L is the instrument preferred by NICE for the assessment of HRQoL, as stated in the NICE Guidelines.[116] As HSUVs in this form were not directly available from patients in the ADAURA trial, mapping from SF-36 onto the EQ-5D-3L index was required.

For the DM1 health state, the EORTC QLQ-C30 from the FLAURA trial were previously mapped to EQ-5D-3L, using a mapping algorithm by Young et al, 2015,[142] which was deemed to fit the observed data well, see FLAURA appraisal (TA654) for more details.[77]

B.3.4.2.1 Mapping methodology

The SF-36 questionnaire was 'translated' to EQ-5D utility scores using the approach of Rowen et al, 2009,[143] which adheres to the guidance set out in NICE TSD 10.[144] Linear regression models were used to estimate the utilities using the generalised least squares (GLS) technique. Rowen et al 2009 conclude the random effects GLS model including SF-36 dimensions, and all squared and interaction terms ('model 3') is the most accurate, and this was used in the analysis.[143] A list of the interaction terms are available in the full utility mapping report;[145] the EQ-5D utility score is the dependent variable. To obtain utility scores, UK-specific preference weights were used to calculate utility values.[146] Observations with missing data were excluded from the analyses, however compliance rates for the SF-36 questionnaire were high (>90%) in the overall ADAURA study population through to Week 144.[3]

B.3.4.2.2 Repeated measures methodology

Exploratory descriptive analyses were carried out using the data, which were additionally used for validation purposes. Baseline utilities were calculated and compared between the osimertinib and placebo (active monitoring) treatment arms. The mean utility per reported cycle was also calculated so that any change in utility over time could be observed, as well as end of treatment and follow-up utilities.

Three covariates were considered in this analysis: AE; baseline utility; and treatment effect. Adverse events were analysed to capture any disutility due to any grade 3 or higher AE and derived such that utilities were accounted for from first onset of the adverse event until death/end of study. Baseline utilities were included to ensure that treatment effect could be measured correctly, as recommended in NICE DSU TSD 12.[147] Regression analyses using repeated measures mixed effect (RMME) models were conducted. This method uses both fixed and random effects, so that the effects of the covariates can be determined while simultaneously correcting for individual patient effects. Note that cycle (24 weeks as time of measurement) is included as random effect in the base case, however cycle is explored as a scenario analysis as fixed effect.

Univariate analyses were also performed to explore the impact of different covariates.

Starting with the full model, including all covariates and their interaction terms with treatment, a backwards stepwise approach was used to remove non-significant predictors at each step until a final model containing only the significant terms were left. A p-value of 0.05 was used to determine statistical significance for each of the predictors. To determine the best fitting

model, the appropriateness was assessed by the AIC and BIC scores. The following outlines the equation used in the base case analysis in R:

lmer (utility ~ AE + baseline + tx + AE*tx + baseline*tx + (1| SUBJID), [dataset])

Abbreviations: SUBJID: subject identification number, AE: adverse events, tx: treatment effect
Note: lmer is a function in the lme4 package of R that allows the estimates of the parameters in linear mixed-effects models to be determined.[148]

Prior to data analysis, validation checks were performed. In the ADAURA trial, there were 682 patients (339 receiving osimertinib; 343 receiving placebo), with 40 grade 3+ AEs (related to treatment) reported (32 in osimertinib; 8 in placebo). These numbers were also found in the data required for analysis and thus passed the validation checks.

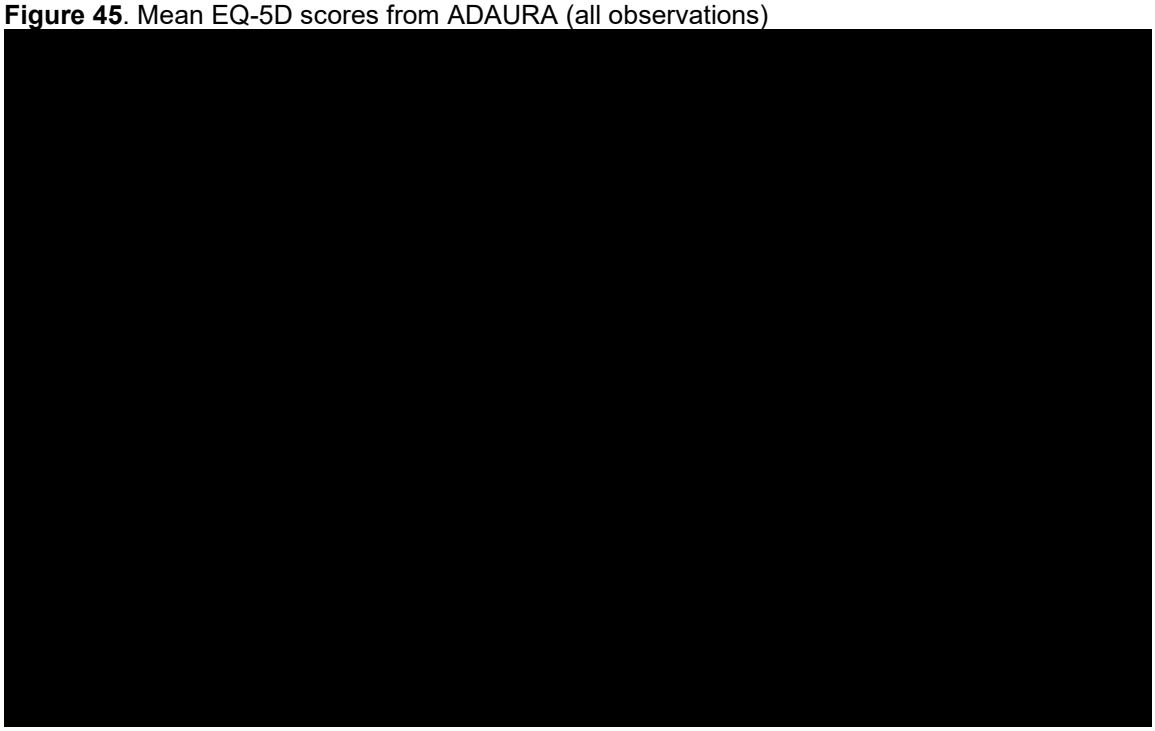
Three scenarios were explored to test the impact of specific variables on utility values: the effect of stage of NSCLC at baseline, defined as stage IB or non-stage IB; the sex of the patient; and the age of the patient. The latter variable was tested using both a linear term, and using an age squared term. For each scenario the descriptive statistics were generated, and a univariate analysis was performed. The main findings of these analyses concluded that the disease stage at baseline did not show a statistically significant effect on utility, however, both sex and age did. However, adding sex and age into the base model selected would not alter the utilities, as in the cost-effectiveness analysis, the mean age and sex (in percentage) from ADAURA are used and thus would recreate the model without age and sex covariates. Further details regarding the scenario analysis is described in the full utility mapping report.[145]

To calculate the mean utility per cycle, the baseline utility, screening and end of treatment (EOT) observations were excluded.

B.3.4.2.3 Results

As shown in Figure 45 and Table 32, the difference between the two treatment populations is minimal. Over time, the mean utility increases for both treatment arms (with comparable patient numbers in each arm), with a decrease seen after 144 weeks. A t-test was performed to test whether the EQ-5D utility values were significantly different in the observations before and after Week 144. This was not significantly different (note that there were 44 placebo patients and 57 osimertinib patients with observations after Week 144), with a p-value of 0.1843.

Figure 45. Mean EQ-5D scores from ADAURA (all observations)



Abbreviations: EOT, end of treatment.

Table 32. Mean EQ-5D scores, from ADAURA

	Tx	*n*	Mean utility	SD
Baseline	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
Day 1	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
12 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
24 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
48 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
72 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
96 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
120 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
144 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]

	Tx	*n*	Mean utility	SD
156 weeks (EOT)	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]

Abbreviations: EOT, end of treatment; SD, standard deviation; Tx, treatment.

Mean utility for observations with or without a grade 3+ AE were also calculated for each treatment arm, the results of which can be seen in Table 33. The utilities are measured from the point of first AE until death or end of follow-up (whichever occurs first). As expected, when an AE was not experienced, mean utility for both treatment arms was higher.

Table 33. Mean utility for observations with or without AE (by treatment arm)

	Treatment	*n*	Mean	SD	Q1	Median	Q3
With CTCAE Grade 3+	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without CTCAE Grade 3+	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Note: *n* here refers to the number of observations, not the number of patients

There were 337 osimertinib patients and 341 placebo patients included in the RMME analyses. The results from the RMME univariate analyses for included covariates (selected as described in Section B.3.4.1) along with their parameter estimates are shown in Table 34.The impact of grade 3+ AE and baseline utility covariates are significant (p-value <0.05). Both values are negative, implying that utility will decrease as a result. In this case for example, if a patient has a utility of 0.7, an AE will cause the utility to drop to 0.673. Treatment effect was found not to be statistically significant (p-value >0.05), thus indicating that there is neither a positive nor negative effect of treatment.

Table 34. RMME univariate analyses results

Model	Intercept	Estimate	SD	t value	p-value
Covariate 1 (AE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariate 2 (Baseline)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Covariate 3 (Treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; RMME, repeated measures mixed effects; SD, standard deviation.

The base case was derived using backwards selection (using steps and AIC/BIC statistics described in Table 35), starting with the full model (model 0) containing the three covariates and the interaction terms with treatment. Treatment effect is highly non-significant, however this cannot be removed before the interaction terms; the non-significant interaction term between adverse events and treatment effect is removed first (model 1). Treatment effect is still non-significant, however as the interaction term between baseline and treatment effect is non-significant as well, this is removed next (model 2). Treatment effect remains non-significant and is then removed. This gives us a final model containing only significant covariates (model 3). Table 36 outlines the parameter estimates obtained using model 3.

Table 35. Backwards selection of RMME model; AIC/BIC statistics

Model	AIC	BIC
0 (Full model with 3 covariates and interaction terms with treatment)	[redacted]	[redacted]
1 (Interaction term between AE and treatment removed)	[redacted]	[redacted]
2 (Interaction term between AE and treatment, and baseline and treatment, removed)	[redacted]	[redacted]
3 (Treatment effect, interaction term between AE and treatment, and baseline and treatment, removed)	[redacted]	[redacted]

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; RMME, repeated measures mixed effect.

Table 36. Parametric estimates for Model 3

	Estimate	SD
Intercept	[redacted]	[redacted]
Covariate 1 (AE)	[redacted]	[redacted]
Covariate 2 (Baseline)	[redacted]	[redacted]

Abbreviations: AE, adverse event; SD, standard deviation.

To calculate the final health state utilities before and after an adverse event, the following equations were used:

Intercept + (baseline coefficient × average baseline)

Intercept + (baseline coefficient × average baseline) + adverse event coefficient

The final health state utility values for the DF health state are shown in Table 37.

Table 37. Final estimated health state utilities for DF health state

	Mean
DF state	[redacted]
DF state including Grade 3+ CTCAE	[redacted]

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events; DF, disease-free.

A diagnostic analysis of predicted EQ-5D utility values against the observed utility values demonstrated predicted values to match the observed values well, confirming the model validity. The model became less robust at more severe EQ-5D utility values (<0.50), similar to the findings of Rowen et al,[143] who attributed this phenomenon to floor effects associated with the SF-36. Nevertheless, the model still provides a good estimation of health state utility values as the impact of this floor effect would be minimal considering [redacted] and associated mapped utility values.

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

A systematic review 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 patients with NSCLC were sought. The original SLR was run for the NICE TA761 (searches run November 2020), and this was updated for this submission (searches run August 2023).

B.3.4.3.1 Original review

Electronic databases were initially searched on 10th November 2020 via the OVID platform using pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and The Cochrane Library. Supplementary searches of public registries and databases, reference lists, previous HTA appraisals, and conference proceedings were performed to identify data not captured in the database search. Full details of the search, and a summary of the included studies, are provided in Appendix H.

Six publications, reporting on five unique studies, met the eligibility criteria and were included in the review.[21,55,149-152] Of these, three studies were RCTs that investigated the impact of adjuvant chemotherapy or gefitinib on HRQoL over time.[55,149,151] The remaining studies were prospective or retrospective observational studies that surveyed patients with early stage resected NSCLC. Four of the five studies had a North American and/or Asian perspective, while only one reported data for Europe, including the UK.[21] All studies considered patients with early stage, resected NSCLC, although one study was further restricted to stage IB–II disease.[55]

The cancer-specific EORTC-QLQ tool was frequently used to measure HRQoL, including the Q30 in two studies,[55,151] whilst the lung cancer-specific LC43 and LC13 versions of the instrument were also considered in one study each. In addition, HRQoL data collected using the disease-specific Lung Cancer Symptom Scale (LCSS), Functional Assessment of Cancer Therapy – Lung (FACT-L), and the generic Trial Outcome Index (TOI), were also presented.

Health state utility values were reported in one study only,[21] and were described using the generic preference-based EQ-5D instrument. Andreas et al, 2018,[21] presented results from the retrospective LuCaBIS study in which 526 patients with resected, stage IB–IIIA NSCLC in France, Germany and the UK were surveyed to collect data describing the HRQoL associated with their current health state. The response rate was 58% (306/526), therefore there is a high risk of response bias in the HRQoL data collected in this study. Patients in the disease-free health state (n=238) reported a mean (95% CI) EQ-5D score of 0.72 (0.68–0.75); the mean EQ-5D score for patients with locoregional recurrence (n=19) was 0.62 (0.51–0.74) and for distant metastasis/terminal disease (n=32), 0.67 (0.55–0.78). The utility value for the distant metastasis state was higher than for locoregional recurrence which is incongruent with the expected relative values for these health states. The data for the later-stage health states were sourced from a small number of patients and therefore the confidence intervals around these estimates were wide, increasing the uncertainty around the accuracy of these values.

The European, early stage resected NSCLC population in the LuCaBIS study is aligned with the scope of the current appraisal and provides a single source for utility values across the

health states (disease-free, locoregional, and metastatic).[21] However, whilst use of the EQ-5D is in line with the reference case, it is not clear which valuation set was used to value health states, therefore it is not clear whether the utilities reported in this study fully meet the requirements of the NICE reference case. In addition, the small sample size used for the later health states limits the reliability of the utilities elicited for these states.

B.3.4.3.2 Updated review

The SLR update search of the databases was conducted on August 30, 2023. A total of four studies were identified that reported on HRQoL in adults with stage IB-IIIA NSCLC EGFRm.[91,111-113,153] Among all studies, two were conducted in China (n=2), one in the US (n=1) and one in Canada (n=1). Studies were based on data derived from clinical trials or already published data (SLRs and HTA appraisals). Verhoek et al reported that the utilities were mapped from SF-36 to SF-12 and from SF-12 to EQ-5D-3L. The other three studies did not state whether the mapping has been done and, if so, the tool used for mapping. All studies reported utilities per health state. Adverse event disutilities were reported in three out of four studies. Two studies out of three reported the same disutility value for grade 3 and above adverse events. In addition, utilities linked to oral and intravenous administration were reported in Li et al., 2021.

B.3.4.4 *Key differences*

A comparison between utility values obtained from published literature and the utility values used in the base case of this analysis (Section B.3.4.6) can only be conducted versus values reported in the Andreas et al, 2018 study,[21] as that is the only paper reporting EQ-5D utility values for the relevant population and health states. The DF utility values reported in Andreas et al, 2018,[21] are somewhat lower than the base case utility scores estimated from ADAURA and used for this appraisal (Table 38), however, it should be noted that these values also vary quite significantly from country to country, with large confidence intervals around the later-stage health states (due to a very small number of patients) suggesting high uncertainty. In addition, there is a high risk of response bias in the utility data from Andreas et al, 2018 as only 58% of participants responded, and it is not clear which valuation set was used to obtain the utility estimates. However, a scenario analysis using the values from Andreas et al, 2018,[21] was nevertheless conducted to explore the impact of using different utilities, with results presented in Section B.3.8.3.

Table 38. Comparison of DF HSUVs

	ADAURA	Andreas et al, 2018[21]
DF health state utility	[redacted]	0.72

Abbreviations: DF, disease-free; HSUV, health state utility value.

B.3.4.5 *Adverse reactions*

Disutilities associated with adverse events were included within the model. Utility values were sourced from the paper by Nafees et al, 2008,[154] and NICE TA653.[85] The study by Nafees et al, 2008,[154] considered HRQoL, as measured by the EQ-5D, in patients with metastatic NSCLC; disutilities used in NICE TA653 were sourced from a clinical trial of patients with EGFR T790M mutation positive advanced NSCLC.[85] The frequency of AEs experienced in each of the treatment arms – based on ADAURA trial data – was used to

calculate a one-off AE disutility for osimertinib (−0.2185) and placebo (active monitoring) (−0.0140). Disutilities occurring as a result of AEs were applied in the first model cycle only, as it is reasonable to assume that treatment-related AEs are most likely to occur shortly after initiating a new therapy.

The AE disutilities and associated frequencies used to estimate treatment-related disutilities used in the model are presented in Table 39.

Table 39. Summary of AE related disutility values applied in cost-effectiveness analysis

AE	Disutility	Frequency	
		Osimertinib	Placebo (active monitoring)
Paronychia	−0.0325	[redacted]	[redacted]
Decreased Appetite	−0.05	[redacted]	[redacted]
Diarrhoea	−0.0468	[redacted]	[redacted]
Stomatitis *	−0.05	[redacted]	[redacted]
ECG QT prolonged **	0	[redacted]	[redacted]
Ejection fraction decreased**	0	[redacted]	[redacted]

Abbreviations: AE, Adverse event; ECG, electrocardiogram.
* Assumed similar to decreased appetite; ** Assumption

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

Given that HRQoL was available from key clinical trial data (ADAURA and FLAURA), and as preferred by NICE, the trial HRQoL data were utilised within the model for all health states.

The base case cost effectiveness analysis used the EQ-5D-3L utility value in the absence of grade 3+ AEs ([redacted]) derived via the mapping analysis of the ADAURA SF-36 data (described in Section B.3.4.2) to represent the disease-free (DF) state. This value was chosen to avoid double-counting of the impact of AEs on HRQoL. Patients who achieved functional cure maintained the same health state utility value as patients in the DF state prior to the cure point of 5 years, since average HRQoL is not expected to differ amongst DF patients.

For the LRR health state, the same health state utility was assumed as for the DF state due to a lack of data in patients with LRR in the ADAURA trial. This simplifying assumption was made as, although in clinical practice it may be anticipated that patients have a lower utility with LRR (Section B.1.3.2.1), data for LRR state were not available from the mapping study (described in Section B.3.4.2) and it was assumed the same value as in the DF state in the model would be highly conservative and thus applicable without bias.

It should be noted that the health state utility value used in the model for the DF state ([redacted]) is slightly higher than the EQ-5D utility value for the age-matched general population for England (0.810 for patients aged 55–64 years).[155] At face value this is counterintuitive, however Nafees et al, 2017 report that the utility of NSCLC patients of all ages with stable disease and no adverse events is 0.84,[156] which is higher than the utility value used for the DF health state in the current model and offers some validation of the choice of utility value.

For the DM1 state, utility values were used based on the progression-free patients in the FLAURA trial. Utility values for these patients were derived using EORTC QLQ-C30 data from the trial mapped to EQ-5D-3L scores using a mapping algorithm by Young et al, 2015,[142] which was deemed to fit the observed data well. Average health state utility values for each patient in each health state across all observations were calculated using the mapped EQ-5D utility scores. These were then used to calculate the average health state utility value across all patients to minimise selection bias, as a simple average across all observations would have provided a greater weighting to those that remained in the progression-free state (i.e. potentially healthier patients). More details on the methods of mapping is provided in the FLAURA appraisal (TA654).[77] In line with the progressed disease state in TA654, the health state utility value for the DM2 state was sourced from a study of lung cancer patients by Labbé et al, 2017.[157]

All utility values used in the base case model are presented in Table 40. Scenario analyses were conducted using the utility values reported by Andreas et al, 2018.[21]

Table 40. Summary of base case utility values for cost-effectiveness analysis

Health state	Utility value	SE	Reference in submission (section and page number)	Source
DF: Osimertinib	[redacted]	0.018	B.3.4.2	ADAURA[3]
DF: Placebo (active monitoring)	[redacted]	0.018	B.3.4.2	ADAURA[3]
LRR: Osimertinib	[redacted]	0.018	B.3.4.2	ADAURA[3]
LRR: Placebo (active monitoring)	[redacted]	0.018	B.3.4.2	ADAURA[3]
DM1: Osimertinib	[redacted]	0.0069	B.3.4.6	FLAURA[100]
DM1: Placebo (active monitoring)	[redacted]	0.0069	B.3.4.6	FLAURA[100]
DM2	0.640	0.03	B.3.4.6	Labbé et al, 2017 [157]

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, locoregional recurrence; SE, standard error.

To adjust for the natural decline in utility with increasing age, the health state utility values were adjusted based on the age of the model population using the regression formula published by Ara and Brazier, 2010.[158]

B.3.4.6.1 Clinical expert assessment of applicability of health state utility values

Expert opinion noted that the overall trial population observed in ADAURA is representative of patients with early-stage EGFR-mutated NSCLC who could expect to receive adjuvant osimertinib in the UK.[37,46] As a result, health state utility values seen in this study are assumed to be reflective of UK clinical practice. In addition, patients in the FLAURA trial were also deemed to be representative of UK clinical practice, based on expert clinical opinion.[46]

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

B.3.5.1 *Resource identification, measurement and valuation studies*

A systematic review was conducted to identify resource use and cost data from the published literature relevant to the decision problem. The original SLR was run for the NICE TA761 (searches run November 2020), and this was updated for this submission (searches run August 2023).

B.3.5.1.1 Original review

Electronic databases were searched on 10th November 2020 via the OVID platform using pre-determined search strategies, and included MEDLINE®, MEDLINE® In-Process, Embase, EconLit, and The Cochrane Library. Supplementary searches of public registries and databases, reference lists, previous HTA appraisals, and conference proceedings were performed to identify data not captured in the database search.

Full details of the search and a summary of included studies are provided in Appendix I.

Four publications were identified as relevant to the decision problem and therefore included in the review.[21,159-161] All four studies were retrospective in nature; three considered patients with stage IB−IIIA NSCLC,[21,160,161] while Ahmad et al, 2017,[159] focused only on stage II NSCLC. Three of the four studies had a US remit, therefore only one study reported data directly relevant to the UK market.[21] The LuCaBIS study by Andreas et al, 2018,[21] evaluated resource use and costs associated with managing patients with resected stage IB–IIIA NSCLC during and after adjuvant therapy, and after disease progression, in three European countries (UK, France and Germany). Resources considered included the frequency of hospitalisations, clinical visits, imaging, and radiotherapy in each disease stage, in addition to estimates of the monthly direct and indirect costs associated with each disease stage.

B.3.5.1.2 Updated review

The SLR update search of the databases was conducted on August 30, 2023. A total of two studies were identified that reported on healthcare resource use/costs in adults with stage IB-IIIA NSCLC EGFRm.[111,113] Both were conducted outside the European perspective (n=1 Canada and n=1 US) and were both based on the ADAURA randomized controlled trial resulting in adjuvant osimertinib being the intervention and placebo/active monitoring as a comparator in both studies. Both studies were sponsored by AstraZeneca.

None of the selected studies reported HCRU data in patients with stage IB-IIIA NSCLC EGFRm. Two studies reported cost data in patients with EGFRm and both referred to direct costs only. Verhoek et al reported direct costs per health state as well as drug acquisition, disease management and adverse event costs separately.[113] Similarly, Lemmon et al reported costs for drug acquisition, EGFR testing, end of life, adverse events, and MRI CNS+ costs.[111]

B.3.5.1.3 Appropriateness of NHS Ref costs/PbR tariffs

NHS reference costs for 2021/22 were used to model costs of chemotherapy administration, adverse events, laboratory tests, radiotherapy, and healthcare resource use such as hospitalisation, clinical visits and imaging procedures.[162]

B.3.5.1.4 Clinical expert assessment of applicability of cost and healthcare resource use values

Expert opinion was sought from six UK clinicians in the 2020 survey to validate the applicability of the healthcare resource use data to UK clinical practice.[46] The clinicians largely agreed with the proposed estimates sourced from Andreas et al, 2018, and preferred these values over the resource use data used in the FLAURA appraisal for the distant metastasis health states. However, most clinicians stated that radiotherapy is not typically administered to patients who are disease-free. Therefore, radiotherapy resource use was set to zero for patients in the DF health state. In addition, for patients who experience CNS metastases, resource use was not reported in the Andreas et al, 2018, study,[21] and thus data specific to brain metastasis was collected from an advanced NSCLC appraisal (NICE TA536) which was also validated and agreed by the clinicians.[163] Finally, although additional surgery is included as an option in the clinical pathway for patients who have LRR, the clinicians stated that only a very small proportion of patients would undergo this surgery in practice, and therefore it was not included in the model.

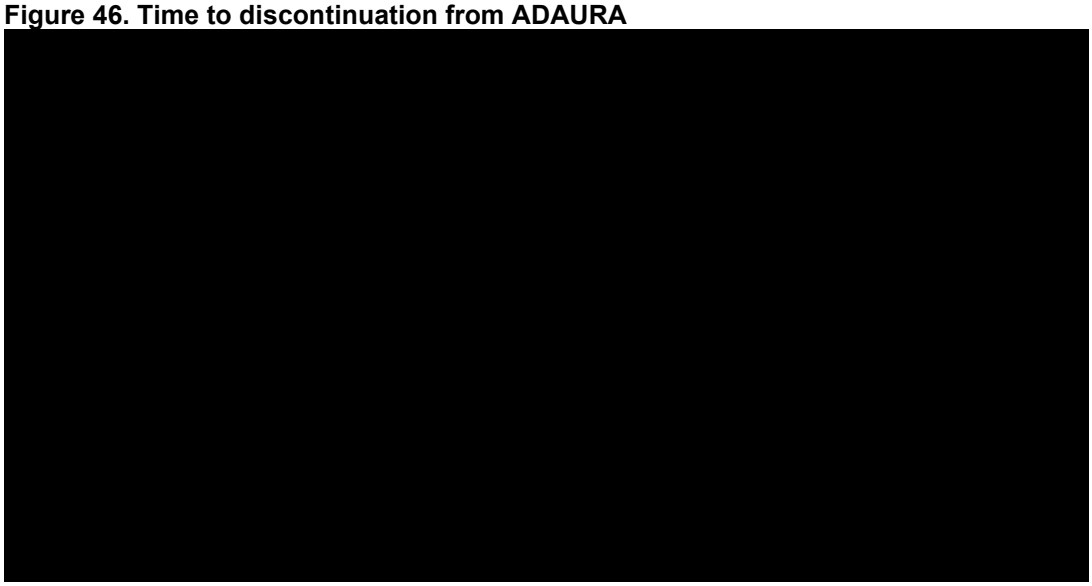
B.3.5.2 *Intervention and comparators' costs and resource use*

B.3.5.2.1 Initial and subsequent therapies

Initial therapy

For the estimation of osimertinib costs in DF, the proportion of patients remaining on osimertinib treatment was based on the observed KM curve for time to treatment discontinuation in the ADAURA study (Figure 46). As per the study protocol, patients randomised to osimertinib received treatment until recurrence of disease, a treatment discontinuation criterion was met, or the 3-year treatment period was completed.[95] Based on this maximum duration, there was sufficient follow-up data from the ADAURA trial to directly observe time on adjuvant treatment, without the need for additional extrapolation.

Figure 46. Time to discontinuation from ADAURA



Subsequent therapy

Treatment of early-stage NSCLC with osimertinib in the adjuvant setting is an innovative development resulting in a step change within the clinical treatment pathway, and therefore the choice and sequence of subsequent therapies used in the metastatic setting is currently uncertainThe clinicians also considered osimertinib to be a more potent and efficacious treatment option compared with other TKIs and thus osimertinib would be the preferred retreatment option.

However, as noted above the uncertainty in treatment sequencing also implies the proportion of patients who would receive retreatment with osimertinib is currently unknown and there have been no clinical studies in the use of osimertinib in patients who have received prior osimertinib treatment in stage IB–IIIA EGFRm NSCLC. It is implausible to assume that all patients would receive retreatment with osimertinib on progression to DM1, therefore in the base case it was assumed that 50% of patients who progressed to metastatic disease after 4 years (48 months) from model entry would be retreated with osimertinib on entry to the DM1 health state, and the remainder (50%) would receive PDC. As per Section B.3.3.6, the 4-year retreatment time point was selected, meaning that patients can be retreated after a 12-month treatment break.[37] Therefore, the model assumes a 12-month treatment break to the end of the three-year treatment duration (i.e. 4 years from surgery). However, scenario analyses are also provided exploring the impact of retreatment at 3.5 and 5 years in the model and the percentage of patients retreated with osimertinib.

Table 41 describes the initial and subsequent therapies applied in the base case analysis per treatment arm and health state. As ADAURA was an internationally-conducted study where osimertinib in DM1 was not consistently reimbursed in every involved country, the subsequent anti-cancer therapies reported in the trial (Appendix Q), were not specifically reflective of UK practice.[3] Therefore, the subsequent therapies included in the model were based on current and expected clinical practice in the UK based on clinical opinion.[46]

In line with NHS guidelines, the duration of subsequent chemotherapy in DM1 and DM2 (i.e. PDC) was assumed to be 5 and 4 treatment cycles of 21 days for PDC and for docetaxel, respectively.[164-167] These treatment cycles were adjusted to the cycle length (i.e. 30.44 days) in the model. Based on UK market share data, patients in the active monitoring arm in DM1 were treated with osimertinib (83%), erlotinib (5%), gefitinib (3%), or afatinib (9%) until progression (in the model that is 444 model cycles, which is then adjusted for the average time to progression). In the LRR state, PDC (4 treatment cycles of 21 days) was also used as part of chemoradiotherapy together with 20 fractions of radiotherapy, which were assumed to be given to patients over 2.8 model cycles based on NICE guidelines.[43] Osimertinib retreatment was given until progression based on the FLAURA trial data used in the DM survival modelling.[100] The NICE Lung Cancer Algorithm for non-squamous NSCLC (2023) suggests that for patients requiring chemotherapy for advanced or metastatic disease (after treatment with osimertinib or other TKIs), the standard treatment is a four-drug regimen of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP). As such, this regimen was applied to 20% of patients in the DM2 health state and was based upon a subgroup of data from the IMPower150 trial with EGFR mutations.[122] Survival models fit to the OS data were used to model the transition to death (as described in Section B.3.3.6.3). For treatment discontinuation, the digitised PFS data was used directly as it was considered relatively complete. The percentage of patients receiving this regimen is in line with data reported by IPSOS prescribing data.[78] This holds for both the efficacy and the costs. The remaining patients receive the costs and efficacy based upon the FLAURA study.

Table 41. Initial and subsequent therapies by treatment arms and health state

Health state	Treatment arm	
	Osimertinib	**Placebo (active monitoring)**
DF	Osimertinib (capped at 36 months [i.e. 36 model cycles])	Placebo (active monitoring)
LRR	PDC + radiotherapy (2.8 model cycles or until progression)	PDC + radiotherapy (2.8 model cycles or until progression)
DM1	Enter DM1 <48 months after initiating adjuvant Osimertinib: PDC: 100% (3.4 model cycles or until progression) Enter DM1 ≥48 months after initiating adjuvant Osimertinib: Osimertinib retreatment: 50% (until progression) PDC: 50% (3.4 model cycles or until progression)	Osimertinib: 83% (until progression) Erlotinib: 5% (until progression) Gefitinib: 3% (until progression) Afatinib: 9% (until progression)
DM2	If retreated with osimertinib in DM1: PDC (3.4 model cycles or until death) or ABCP: 20% (2.8 cycles or until death, with maintenance AB until progression) If not retreated with osimertinib in DM1 (i.e. received PDC): Docetaxel (2.8 model cycles or until death)	PDC (3.4 model cycles or until death)

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, locoregional recurrence; PDC, pemetrexed plus cisplatin.
The duration of each subsequent therapy in each health state is given in parentheses.

B.3.5.2.2 Drug acquisition and other therapy costs

Drug acquisition costs were sourced from the BNF and eMIT databases and are displayed in Table 42. Where multiple generic forms of a drug were available, the cheapest generic form was used for the base case.

Table 42. Drug acquisition costs

Drug	Vial size/ tablet dose	Pack size	Cost per pack	Source
Osimertinib – initial use	80 mg	30	[redacted] (list price: £5,770)	BNF 2023[168]
Osimertinib – use in metastatic setting	80 mg	30	[redacted] (list price: £5,770)	BNF 2023[168]
PDC: Pemetrexed	100 mg	1	£29.11	eMIT 2023[169]
PDC: Cisplatin	50 mg	1	£5.58	eMIT 2023[169]
Docetaxel	80 mg	1	£8.17	eMIT 2023[169]
Erlotinib	150 mg	30	£98.99	eMIT 2023[169]
Gefitinib	250 mg	30	£285.08	eMIT 2023[169]
Afatinib	40 mg	28	£2,023.28	BNF 2023[168]
ABCP: Atezolizumab	1200 mg	1	£3,807.69	BNF 2023[168]
ABCP: Bevacizumab	400 mg	1	£810.00	BNF 2023[168]
ABCP: Paclitaxel	300 mg	1	£17.40	eMIT 2023[169]
ABCP: Carboplatin	600 mg	1	£21.54	eMIT 2023[169]

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; PDC, pemetrexed, cisplatin.

As radiotherapy is part of the treatment sequence, the unit cost is presented in Table 43.

Table 43. Radiotherapy unit cost

Resource	Unit cost	Source[162]
Radiotherapy fraction	£211.85	NHS Reference costs 2021/22: SC23Z - Deliver a Fraction of Complex Treatment on a Megavoltage Machine
Cost of planning meetings	£ 1,174.46	NHS Cost collection 2021/22. SC52Z, Preparation for Complex Conformal Radiotherapy, with Technical Support

Abbreviations: NHS, National Health Service.

B.3.5.2.3 Dosing

Drug dosing and acquisition costs per model cycle are presented in Table 44. Details of the dosing regimen for osimertinib were sourced from the ADAURA trial and were in line with the label. Dosing information for subsequent therapies were aligned with TA654 for osimertinib in first-line metastatic NSCLC.[77] Dose per treatment cycle was calculated based on the dose

per administration, the number of administrations per treatment cycle, and the duration of the treatment cycle for each therapy, and then adjusted for the 30.44-day model cycle length.

Average dosages for pemetrexed, cisplatin and docetaxel were calculated based on an average body surface area (BSA) of 1.67 m^2, calculated for the UK population combined with the Gehan and George formula.[170] For the base case analysis, vial-sharing for intravenous chemotherapy was assumed to occur, therefore wastage costs were excluded.

In practice, the actual dose delivered may differ from the planned dose per treatment cycle due to missing or delayed doses and toxicity-related dose reductions. To reflect the ratio of actual to scheduled drug delivery, relative dose intensity (RDI) adjustments were applied to the planned dose per cycle. As patients are more likely to miss, postpone or receive smaller doses than to receive additional doses per cycle the assumption was made, in the model, that the RDI is bounded between 0% and 100%. Where RDIs were not reported from the relevant clinical trials, assumptions were made as noted in the table below.

Table 44. Drug dosing and acquisition costs per cycle

Drug	Dose per administration	Administrations per treatment cycle	Treatment cycle duration, days	Relative dose intensity	Cost per model cycle
TKI					
Osimertinib – initial use	80 mg	30	30	[redacted]	[redacted]
Osimertinib – use in metastatic setting	80 mg	30	30	[redacted]	[redacted]
Erlotinib	150 mg	30	30	98.1%	£98.53
Gefitinib	250 mg	30	30	98.1%	£283.75
Afatinib	40 mg	28	28	98.1%	£2,157.62
PDC					
Pemetrexed	500 mg/m^2	1	21	100%‡	£352.26
Cisplatin	75 mg/m^2	1	21	100%‡	£20.27
Radiotherapy					
Radiotherapy* – in LRR	55 Gray	20 fractions	21	-	£5,411.43
Chemoradiotherapy					
Chemoradiotherapy¥ – in LRR	-	-	21	-	£2,333.36
Single chemotherapy					
Docetaxel	75 mg/m^2	1	21	100%‡	£18.54
ABCP					
Atezolizumab	1200 mg	1	21	100%	£5,518.88
Bevacizumab	15 mg/ kg	1	21	100%	£2,773.62
Carboplatin	692 mg	1	21	100%	£36.00
Paclitaxel	200 mg/ m2	1	21	100%	£28.08

Abbreviations: ABCP, atezolizumab, bevacizumab, carboplatin, paclitaxel; LRR, Locoregional recurrence; PDC, pemetrexed, cisplatin; TKI, tyrosine kinase inhibitor.
† Assumption – Equivalent to SoC in FLAURA; ‡ Assumption; § FLAURA trial;*Includes cost of delivery of radiotherapy and planning meetings; ¥Includes radiotherapy and PDC

B.3.5.2.4 Drug administration costs

For oral therapies (osimertinib), administration costs were assumed to be the cost of a pharmacist dispensing the drug and were sourced from the PSSRU,[171] based on 12 minutes of pharmacist time to align with the ERG's recommendations in TA654.[77] Chemotherapy administration costs (for pemetrexed, cisplatin and docetaxel) were sourced from NHS Reference costs 2021/22, considering an outpatient attendance for delivery of 'complex chemotherapy including prolonged infusion treatment.[162] Costs were entered separately for first and subsequent chemotherapy sessions. In addition, the cost of premedication with dexamethasone at 8 mg per day (or 16 mg per day for docetaxel) for 3 days, sourced from eMIT,[169] was added to the administration cost of chemotherapy treatments. The drug administration costs applied in the model are described in Table 45.

Table 45. Drug administration costs

Drug	Administration	Unit cost	Cost per first administration	Cost per subsequent administration	Source
Osimertinib, Erlotinib, Gefitinib, or Afatinib	Band 6 pharmacist dispensing (12 mins)	£53 per hour	£10.60	£10.60	PSSRU 2022[171]
PDC, cisplatin or pemetrexed	Deliver complex chemotherapy, including prolonged infusional treatment – outpatient (SB14Z) – First attendance	£485.23	£485.86	£384.16	NHS Reference costs 2021/22[162]
	Deliver Subsequent Elements of a Chemotherapy Cycle - SB15Z	£383.54			NHS Reference costs 2021/22[162]
	Dexamethasone (premedication), 8 mg per day for 3 days, £0.63	£2.62 per 50 x 2 mg pack			eMIT 2023[169]
Docetaxel	Deliver complex chemotherapy, including prolonged infusional treatment – outpatient (SB14Z) – First attendance	£485.23	£486.49	£384.79	NHS Reference costs 2021/22[162]

Drug	Administration	Unit cost	Cost per first administration	Cost per subsequent administration	Source
	Deliver Subsequent Elements of a Chemotherapy Cycle - SB15Z	£383.54			NHS Reference costs 2021/22[162]
	Dexamethasone (premedication), 16 mg per day for 3 days, £1.26	£2.62 per 50 x 2 mg pack			eMIT 2023[169]
Atezolizumab plus bevacizumab, carboplatin and paclitaxel	Deliver complex chemotherapy, including prolonged infusional treatment – outpatient (SB14Z) – First attendance	£485.23	£485.86	£384.16	NHS Reference costs 2021/22[162]
	Deliver Subsequent Elements of a Chemotherapy Cycle – SB15Z	£363.09			NHS Reference costs 2021/22[162]
	Dexamethasone (premedication), 8 mg per day for 3 days, £0.63	£2.62 per 50 x 2 mg pack			eMIT 2023[169]

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

B.3.5.2.5 Monitoring costs

Regular biochemistry and haematology testing costs, sourced from NHS Reference costs 2021/22 were applied in each model cycle to patients on the treatment. It was assumed that patients treated with osimertinib in the DF state require less monitoring than patients treated with osimertinib in the DM state. The costs (see Table 46) and frequency (see Table 47) are specified per treatment.

Table 46. Monitoring costs

Test	Unit cost	Source[162]
Liver function test	£1.55	NHS Reference costs 2021/22
Renal function test	£1.55	
Complete blood count	£2.96	
ECG	£159.36	
Echocardiogram	£363.09	

Abbreviations: ECG, electrocardiogram

Table 47. Frequency of monitoring, per treatment

	Osimertinib (DFS)	Osimertinib (DM1)	EGFR-TKI (DM1/ DM2)	Chemo	Docetaxel	ACBP
Liver function test	36%	72%	72%	100%	100%	100%
Renal function test	36%	72%	72%	100%	100%	100%
Complete blood count	36%	72%	72%	100%	100%	100%
ECG	36%	72%	72%	-	-	-
Echocardiogram	36%	72%	72%	-	-	-

Abbreviations: DFS, disease-free survival; EGFR-TKI, osimertinib (DM1), afatinib, gefitinib, erlotinib, dacomitinib; Chemo, PDC, pemetrexed, cisplatin; ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel.

B.3.5.3 *Health-state costs and resource use*

Healthcare resource use data relating to clinical visits, hospitalisation, and imaging for each of the alive model health states were sourced from the LuCaBIS study by Andreas et al, 2018,[21] identified in the systematic review. The study evaluated resource use and costs associated with managing patients with resected stage IB–IIIA NSCLC during and after adjuvant therapy, and after disease progression to LRR or distant metastasis, in three European countries. The UK-specific data for each health state were adjusted by the time spent in each health state to calculate the average resource use per 28-day model cycle. These data were verified by six UK clinical experts,[46] and resource use estimates per cycle are presented in Table 48.

For the DF health state, Andreas et al, 2018[21] reported resource use separately for patients on adjuvant chemotherapy and patients not on adjuvant chemotherapy. The HCRU estimates from Andreas et al, 2018 and the FLAURA appraisal (TA654) were validated with six UK clinical experts in the 2020 surveys, who indicated that DF patients not on adjuvant chemotherapy would not attend oncologist visits, and that radiotherapy would not be given to patients in the DF state.[46] The values from Andreas et al. 2018 were amended accordingly. The resource use inputs for the DF health state were then calculated by taking the average resource use for DF patients on or off adjuvant chemotherapy. In line with input from the clinical experts, patients who achieved a

functional cure were assumed to be discharged from the oncology service and therefore the health state costs applied to these patients after the cure point were set to zero. Resource use was assumed to be equivalent between the DM1 and DM2 states as the data in Andreas et al, 2018[21] did not distinguish between these patient groups (Table 48). This is a conservative assumption as costs in DM2 state are likely to be higher than in DM1, and as patients in the placebo (active monitoring) arm transition to DM1 and DM2 states more quickly, it favours the placebo (active monitoring) arm in the model.

Unit costs for healthcare resources were sourced from NHS Reference costs 2021/22[162] and are presented in Table 49. A summary of the total health state costs is provided in Table 50.

Table 48. Healthcare resource use, by health state

	Healthcare resource use per model cycle[21]			
	DFS†	**Loco-regional recurrence**	**1st line distant metastases**	**2nd line distant metastases**
Hospitalisation	0.069	0.120	0.207	0.207
Oncologist visits (subsequent)	0.086‡	0.635	0.609	0.609
Surgeon visits	0.151	0.184	0.149	0.149
Pulmonologist/ respiratory physician (subsequent)	0.153	0.239	0.115	0.115
Other specialist visit	0.146	0.230	0.149	0.149
Emergency room	0.065	0.120	0.161	0.161
CT scans	0.079	0.202	0.264	0.264
MRI	0.044	0.092	0.138	0.138
PET scans	0.046	0.092	0.230	0.230
PET-CT scans	0.065	0.092	0.115	0.115
Ultrasound	0.069	0.092	0.149	0.149
Nuclear medicine studies	0.021	0.092	0.115	0.115

† Average of DFS patients on adjuvant chemotherapy and not on adjuvant chemotherapy; ‡ Oncologist visits for patients not on adjuvant chemotherapy set to zero based on KOL input.
Abbreviations: CT, computed tomography; DFS, disease-free survival; KOL, key opinion leader; MRI, magnetic resonance imaging; PET, positron emission tomography.

Table 49. Healthcare resource use unit costs

Resource	Unit cost	Source[162]
Hospitalisation	£827.06	NHS Reference costs 2021/22: DZ19H-N - Other Respiratory Disorders with/without Single/Multiple Interventions, with CC Score 0-11+; Non-elective long and short stay (weighted average)
Oncologist visits (subsequent)	£163.79	NHS Reference costs 2021/22: 800 - Clinical Oncology (Previously Radiotherapy) consultant led outpatient attendance

Resource	Unit cost	Source[162]
Surgeon visits	£242.72	NHS Reference costs 2021/22: 173 - Thoracic Surgery consultant led outpatient attendance
Pulmonologist/ respiratory physician (subsequent)	£194.75	NHS Reference costs 2021/22: 340 - Respiratory medicine consultant led outpatient attendance
Other specialist visit	£163.79	Assuming it costs the same as a visit to a clinical oncologist: 800 - Clinical Oncology (Previously Radiotherapy) consultant led outpatient attendance
A&E visits	£157.62	NHS Reference costs 2021/22: 180 - Accident & Emergency consultant led outpatient attendance
CT scans	£142.47	NHS Reference costs 2021/22: RD24Z - Computerised Tomography Scan of two areas, with contrast
MRI	£243.18	NHS Reference costs 2021/22: RD05Z - Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
PET scans	£665.48	NHS Reference costs 2021/22: RN07A - Positron Emission Tomography (PET), 19 years and over
PET-CT scans	£722.11	NHS Reference costs 2021/22: RN01A/RN02A/RN03A - Positron Emission Tomography with Computed Tomography (PET-CT) of One/Two or Three/more than Three Area, 19 years and over (weighted average)
Ultrasound	£84.95	NHS Reference costs 2021/22: RD41Z/RD43Z - Ultrasound Scan with duration of less than 20 minutes/20 minutes and over, with Contrast (weighted average)
Nuclear medicine studies	£165.38	NHS Reference costs 2021/22: 371 - Nuclear medicine, consultant led outpatient attendance

Abbreviations: A&E, accident and emergency; CT, computed tomography; DFS, disease-free survival; MRI, magnetic resonance imaging; NHS, National Health Service; PET, positron emission tomography.

Table 50. Healthcare resource use, cost per health state per model cycle

Health state	Cost
DF	£280.20
LRR	£552.51
DM1	£718.58
DM2	£718.58

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; LRR, locoregional recurrence.

In the ADAURA trial, 51 patients in the osimertinib arm experienced distant metastatic disease recurrence compared to 127 patients in the placebo arm. From these, 22 patients experienced CNS disease recurrence in the osimertinib arm (equating to 43.1%) and 39 patients experienced CNS disease recurrence in the placebo arm (equating to 30.7%)Additional resources for patients in the distant metastases health states were

applied to the proportion of patients with CNS metastases to capture the additional burden of this complication (Table 51). Resource use frequencies were sourced from NICE TA536,[163] adjusted for the baseline DM resource use and costs described above and the 30.44-day model cycle length. Costs related to the additional resource use due to CNS metastasis were estimated using unit costs from the NHS Reference costs[162] and PSSRU 2022[171] and applied as an incremental cost to a proportion of patients with CNS metastasis in the DM states. Based on clinical expert opinion (both from NICE TA536[163] and six UK clinicians interviewed in the 2020 surveys)[46] and a publication by the Royal College of Radiologists, 2019,[172] these patients were also assumed to receive stereotactic or whole brain radiotherapy which was applied as a one-off cost when patients entered the DM1 health state (Table 52).

Table 51. Additional healthcare resource use and costs associated with CNS metastasis

Resource	Frequency per cycle	Unit cost	Source
Consultant/Oncologist outpatient visit	0.6	£163.79	NHS Reference costs 2021/22: 800 - Clinical Oncology (Previously Radiotherapy) consultant led outpatient attendance[162] NICE TA536 (ID925)[163]
GP visit	0.9	£41.00	PSSRU 2022: GP consultation lasting 9.22 minutes (with qualification costs)[171] NICE TA536 (ID925)[163]
Cancer nurse visit	1.4	£119.00	NHS Reference costs 2021/22: N10AF - Specialist Nursing, Cancer Related, Adult, Face to face[162] NICE TA536 (ID925)[163]
Full blood test	1.4	£2.96	NHS Reference costs 2021/22: DAPS05 – Haematology[162] NICE TA536 (ID925)[163]
Biochemistry	1.4	£1.55	NHS Reference costs 2021/22: DAPS04 – Clinical biochemistry[162] NICE TA536 (ID925)[163]
CT scan	0.4	£160.38	NHS Reference costs 2021/22: RD26Z - Computerised Tomography Scan of three areas, with contrast[162] NICE TA536 (ID925)[163]
MRI scan	0.3	£243.18	NHS Reference costs 2021/22: RD05Z - Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast[162] NICE TA536 (ID925)[163]
X-ray	0.5	£38.28	NHS Reference costs 2021/22: DAPF - Direct Access Plain Film[162] NICE TA536 (ID925)[163]
Total	**-**	£477.21	

Abbreviations: CT, computed tomography; GP, general practitioner; MRI, magnetic resonance imaging.

Table 52. Radiotherapy costs in CNS metastasis

Radiotherapy approach	% of patients	Doses	Unit cost	Source
Stereotactic radiotherapy	50%	6	£5,456.83	Royal College of Radiologists 2019[172] NHS Reference costs 2021/22: AA71A-B - Stereotactic Intracranial Radiosurgery, for Neoplasms or Other Neurological Conditions, with CC Score 0-4+; Elective (weighted average)[162]
Whole brain radiotherapy	50%	1	£4,491.28	Royal College of Radiologists 2019 [172] ERG report for NICE ID925 (TA536)† [163]

Abbreviations: CNS, central nervous system; ERG, Evidence review group; NHS, National Health Service.
† Inflated from 2017 to 2023, using NHSCII.

In addition, one-off terminal care costs are applied to all patients in the model when they transition to the death state to capture healthcare costs at the end of life (Table 53). The terminal care cost is calculated based on the proportion of patients who receive end of life care in hospital, in a hospice, or at home, sourced from a study by Brown et al, 2015.[173] Cost inputs were sourced from NHS Reference costs 2021/22,[162] the PSSRU 2022,[171] and a Marie Curie report.[174]

Table 53. Terminal care costs

Terminal care in:	% of patients[173]	Unit cost	Source
Hospital	55.8%	£2,878.29	DZ17L-V - Respiratory Neoplasms with/without Single/Multiple Interventions, with CC Score 0-13+; Non-elective long and short stay (weighted average). NHS Reference Costs 2021/22[162]
Hospice	16.9%	£3,597.86	Assuming 25% increase on hospital inpatients care
Home	27.3%	£2,153.35	28 hours community nurse visit including travel time: N02AF - District Nurse, Adult, Face to face (NHS Reference Costs 2021/22; £53.74 per hour)[162] 7 GP home visits including travel time: Per patient contact lasting 9.22 minutes including carbon emissions (incl. qualification and direct staff costs) (PSSRU 2022; £41)[171] Drugs and equipment - Marie Curie report figure of £240 (2003/04)[174] updated to 2021/22 value using HCHS and NHSCII from PSSRU 2010 and 2022[171]
Total	**-**	**£2,801.99**	

Abbreviations: CC, complexity and comorbidity; HCHS, Hospital and Community Health Service; NHS, National Health Service; NHSCII, National Health Service Cost Inflation Index; PSSRU, Personal Social Services Research Unit.

B.3.5.4 *Adverse reaction unit costs and resource use*

Grade 3 or higher, causally related to treatment AEs that occurred in at least two patients in either treatment arm in the ADAURA trial were included in the model. Where data were not reported for an AE, the value in the model was set to zero. Based on these criteria, six AEs were eligible for inclusion. The costs of managing AEs were applied as one-time costs in the first cycle of the model and were all sourced from the NHS Reference Costs 2021/22 (Table 54).[162] Adverse events were not modelled post-progression (LRR, DM1, DM2) for both cost and utility, which is seen as a conservative assumption seeing that the including of costs associated with AEs from downstream treatments would be higher for the comparator group.

Table 54. Adverse event costs

Grade 3-4 adverse event	Incidence[3]		Cost input	Source[162]
	Osimertinib	Placebo (active monitoring)		
Paronychia	0.9%	0.0%	£2,011.95	JD07A-K Skin Disorders with/without Interventions, with CC Score 0–19+; Non-elective long and short stay (weighted average)
Decreased Appetite	0.6%	0.0%	£2,639.41	Nutritional Disorders with/without Interventions, with CC Score 0–2+; Non-elective long and short stay (weighted average)
Diarrhoea	2.1%	0.3%	£1,847.25	FD10A-M Non-Malignant Gastrointestinal Tract Disorders with/without (single/multiple) Interventions, with CC Score 0–9+; Non-elective long and short stay (weighted average)
Stomatitis	1.5%	0.0%	£1,273.81	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with/without Interventions, with CC Score 0–5+; Non-elective long and short stay (weighted average)
ECG QT prolonged	1.2%	0.3%	£2,399.26	Other Acquired Cardiac Conditions with CC Score 0–13+; Non-elective long and short stay (weighted average)
Ejection fraction decreased	0.6%	0.3%	£3,201.01	EB06A-D, Cardiac Valve Disorders with CC Score 0-13+; Non-elective long and short stay (weighted average)

Abbreviations: CC, complexity and comorbidity; ECG, electrocardiogram.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 *Summary of base-case analysis inputs*

A list of all variables estimated and used in the economic analysis is provided in Table 55. The confidence intervals and distributions used to vary these parameters in the sensitivity analyses are provided in Appendix N.

Table 55. Summary of variables applied in the economic model

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
General model parameters				
Time horizon	37 years	Fixed	B.3.2.2	Lifetime time horizon
Discount rate - efficacy	3.50%	Fixed	B.3.2.2	NICE Reference case, 2013
Discount rate - costs	3.50%	Fixed	B.3.2.2	NICE Reference case, 2013
Age (median)	63 years	Fixed	B.3.2.2	ADAURA
% male	30%	Fixed	B.3.2.2	ADAURA
Body surface area (BSA)	1.67m^2	Normal (0.167)	B.3.2.1	UK population combined with the Gehan and George formula (0.01545*(height^0.54468)*(weight^0.46336))
Osimertinib retreatment timepoint	4 years	Varied in scenario analyses	B.3.3.6	Expert clinical opinion
Osimertinib retreatment percentage	50%	Varied in scenario analyses	B.3.3.6	Assumption
Survival distributions				
DF to LRR (TP1) - Osimertinib	Lognormal	Cholesky decomposition	B.3.3.3.2	ADAURA
DF to LRR (TP1) – Placebo (active monitoring)	Lognormal	Cholesky decomposition	B.3.3.3.2	ADAURA
DF to DM1 (TP2) - Osimertinib	Loglogistic	Cholesky decomposition	B.3.3.3.3	ADAURA
DF to DM1 (TP2) – Placebo (active monitoring)	Lognormal	Cholesky decomposition	B.3.3.3.3	ADAURA

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
DF to Death (TP3) - Osimertinib	Exponential	Cholesky decomposition	B.3.3.3.4	UK Life Table
DF to Death (TP3) – Placebo (active monitoring)	Exponential	Cholesky decomposition	B.3.3.3.4	UK Life Table
LRR to DM1 (TP4) - Osimertinib	Lognormal	Cholesky decomposition	B.3.3.5.1	CancerLinQ
LRR to DM1 (TP4) – Placebo (active monitoring)	Lognormal	Cholesky decomposition	B.3.3.5.1	CancerLinQ
LRR to Death (TP5) - Osimertinib	Exponential	Cholesky decomposition	B.3.3.5.2	UK Life Table
LRR to Death (TP5) – Placebo (active monitoring)	Exponential	Cholesky decomposition	B.3.3.5.2	UK Life Table
DM1 to DM2 (TP6) - Osimertinib	Weibull	Cholesky decomposition	B.3.3.6.1	FLAURA
DM1 to DM2 (TP6) - Placebo	Weibull	Cholesky decomposition	B.3.3.6.1	FLAURA
DM1 to Death (TP7) - Osimertinib	Exponential	Cholesky decomposition	B.3.3.6.2	FLAURA / UK Life Table
DM1 to Death (TP7) – Placebo (active monitoring)	Exponential	Cholesky decomposition	B.3.3.6.2	FLAURA / UK Life Table
DM2 to Death (TP8) - Osimertinib	Weibull	Cholesky decomposition	B.3.3.6.3	FLAURA

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
DM2 to Death (TP8) – Placebo (active monitoring)	Weibull	Cholesky decomposition	B.3.3.6.3	FLAURA
Cure parameters				
Cure timepoint	0% in year 4, gradually increasing to 95% in year 8 and year 5, Osimertinib and active surveillance, respectively	Varied in scenario analyses	B.3.3.3.1	KOL input; Assumption
Cure percentage	95%	Varied in scenario analyses	B.3.3.3.1	KOL input; Assumption
Drug acquisition costs (per model cycle), osimertinib arm				
Vial sharing assumed	No	Fixed	B.3.5.2.2	Assumption
DF: Osimertinib	[redacted]	Gamma ([redacted])	B.3.5.2.2	AZ data on file
LRR				
Chemoradiotherapy	£2,333.36	Gamma (233.34)	B.3.5.2.2	NHS Reference Costs 2021/22, eMIT 2023
Radiotherapy	£5,411.43	Gamma (541.14)	B.3.5.2.2	NHS Reference Costs 2021/22
DM1				
No retreatment: PDC	£372.52	Gamma (37.25)	B.3.5.2.2	BNF 2023, eMIT
Retreatment: Osimertinib	[redacted]	Gamma ([redacted])	B.3.5.2.2	AZ data on file
DM2				
Received osimertinib at DM1: PDC	£372.52	Gamma (37.25)	B.3.5.2.2	BNF 2023, eMIT

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Received PDC at DM1: Docetaxel	£18.54	Gamma (1.85)	B.3.5.2.2	eMIT
Received osimertinib at DM1: ABCP - Atezolizumab	£5,518.88	Gamma (551.89)	B.3.5.2.2	BNF 2023, eMIT
Received osimertinib at DM1: ABCP - Bevacizumab	£2,773.62	Gamma (277.36)	B.3.5.2.2	BNF 2023, eMIT
Received osimertinib at DM1: ABCP - Carboplatin	£36.00	Gamma (3.60)	B.3.5.2.2	BNF 2023, eMIT
Received osimertinib at DM1: ABCP - Paclitaxel	£28.08	Gamma (2.81)	B.3.5.2.2	BNF 2023, eMIT
Drug acquisition costs (per model cycle), placebo (active monitoring) arm				
DF: Placebo (active monitoring)	£0	Gamma (0)	B.3.5.2.2	-
LRR				
Chemoradiotherapy	£2,333.36	Gamma (233.34)	B.3.5.2.2	NHS Reference Costs 2021/22, eMIT 2023
Radiotherapy	£5,411.43	Gamma (541.14)	B.3.5.2.2	NHS Reference Costs 2021/22
DM1				
Osimertinib	[redacted]	Gamma ([redacted])	B.3.5.2.2	AZ data on file
Erlotinib	£98.53	Gamma (9.85)	B.3.5.2.2	eMIT
Gefitinib	£283.75	Gamma (28.38)	B.3.5.2.2	eMIT
Afatinib	£2,157.62	Gamma (215.76)	B.3.5.2.2	BNF 2023

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
DM2				
Received osimertinib at DM1: PDC	£372.52	Gamma (37.25)	B.3.5.2.2	BNF 2023, eMIT
Received osimertinib at DM1: ABCP - Atezolizumab	£5,518.88	Gamma (551.89)	B.3.5.2.2	BNF 2023, eMIT
Received osimertinib at DM1: ABCP - Bevacizumab	£2,773.62	Gamma (277.36)	B.3.5.2.2	BNF 2023, eMIT
Received osimertinib at DM1: ABCP - Carboplatin	£36.00	Gamma (3.60)	B.3.5.2.2	BNF 2023, eMIT
Received osimertinib at DM1: ABCP - Paclitaxel	£28.08	Gamma (2.81)	B.3.5.2.2	BNF 2023, eMIT
Administration costs per model cycle				
First cycle				
TKI/Osimertinib	£396.82	Gamma (39.68)	B.3.5.2.2	PSSRU 2022
Docetaxel	£713.89	Gamma (71.39)	B.3.5.2.2	NHS Reference Costs 2021/22
PDC	£713.89	Gamma (71.39)	B.3.5.2.2	NHS Reference Costs 2021/22
ABCP	£565.58	Gamma (56.56)	B.3.5.2.2	NHS Reference Costs 2021/22
Subsequent cycles				
Osimertinib	£396.82	Gamma (39.68)	B.3.5.2.2	PSSRU 2022
Docetaxel	£566.49	Gamma (56.65)	B.3.5.2.2	NHS Reference Costs 2021/22

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
PDC	£565.58	Gamma (56.56)	B.3.5.2.2	NHS Reference Costs 2021/22
ABCP	£565.58	Gamma (56.56)	B.3.5.2.2	NHS Reference Costs 2021/22
Adverse event costs (per event)				
Paronychia	£2,011.95	Gamma (201.20)	B.3.5.4	NHS Reference Costs 2021/22
Decreased appetite	£2,639.41	Gamma (263.94)	B.3.5.4	NHS Reference Costs 2021/22
Diarrhoea	£1,847.25	Gamma (184.73)	B.3.5.4	NHS Reference Costs 2021/22
Stomatitis	£1,273.81	Gamma (127.38)	B.3.5.4	NHS Reference Costs 2021/22
ECG QT prolonged	£2,399.26	Gamma (239.93)	B.3.5.4	NHS Reference Costs 2021/22
Ejection Fraction Decreased	£3,201.01	Gamma (320.10)	B.3.5.4	NHS Reference Costs 2021/22
Adverse events (%)				
Osimertinib				
Paronychia	[redacted]	Beta (0.0009)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Decreased appetite	[redacted]	Beta (0.0006)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Diarrhoea	[redacted]	Beta (0.0021)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Stomatitis	[redacted]	Beta (0.0015)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
ECG QT prolonged	[redacted]	Beta (0.0012)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Ejection Fraction Decreased	[redacted]	Beta (0.0006)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Placebo (active monitoring)				
Paronychia	[redacted]	Beta (0)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Decreased appetite	[redacted]	Beta (0)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Diarrhoea	[redacted]	Beta (0.0003)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Stomatitis	[redacted]	Beta (0)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
ECG QT prolonged	[redacted]	Beta (0.0003)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Ejection Fraction Decreased	[redacted]	Beta (0.0003)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Utilities				
Osimertinib (DF)	[redacted]	[redacted]	B.3.4.3	ADAURA

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Placebo (active monitoring) (DF)	[redacted]	Beta ([redacted])	B.3.4.3	ADAURA
Osimertinib (LRR)	[redacted]	Beta ([redacted])	B.3.4.3	ADAURA
Placebo (active monitoring) (LRR)	[redacted]	Beta ([redacted])	B.3.4.3	ADAURA
Osimertinib (DM1)	[redacted]	Beta ([redacted])	B.3.4.3	FLAURA
Placebo (active monitoring) (DM1)	[redacted]	Beta ([redacted])	B.3.4.3	FLAURA
DM2	0.64	Beta (0.03)	B.3.4.3	Labbé et al, 2017
Disutility (due to AEs)				
Paronychia	-0.0325	Beta (-0.00163)	B.3.4.5	FLAURA
Decreased appetite	-0.05	Beta (-0.0025)	B.3.4.5	NICE TA653
Diarrhoea	-0.0468	Beta (-0.00234)	B.3.4.5	Nafees (2008)
Stomatitis	-0.05	Beta (-0.0025)	B.3.4.5	Assumption
ECG QT prolonged	0	Beta (0)	B.3.4.5	Assumption
Ejection Fraction Decreased	0	Beta (0)	B.3.4.5	Assumption
Age-adjustment regression coefficients				
Base	0.9572	Beta (0.02)	B.3.4.6	Ara and Brazier 2010
Age	-0.0003	Beta (0.000013)	B.3.4.6	Ara and Brazier 2010
Age squared	0.0000	Beta (0.0000017)	B.3.4.6	Ara and Brazier 2010
HCRU costs per cycle				
DF				

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Hospitalisation	£57.06	Gamma (5.71)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Oncologist visits (subsequent)	£14.04	Gamma (1.40)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Surgeon visits	£36.54	Gamma (3.65)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Pulmonologist/ respiratory physician (subsequent)	£29.72	Gamma (2.97)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Other specialist visit	£23.90	Gamma (2.39)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Emergency room	£10.22	Gamma (1.02)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
CT scans	£11.32	Gamma (1.13)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
MRI	£10.68	Gamma (1.07)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET scans	£30.61	Gamma (3.06)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET-CT scans	£46.80	Gamma (4.68)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Ultrasound	£5.86	Gamma (0.59)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Nuclear medicine studies	£3.46	Gamma (0.35)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Loco-regional recurrence				

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Hospitalisation	£98.91	Gamma (9.89)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Oncologist visits (subsequent)	£103.97	Gamma (10.40)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Surgeon visits	£44.66	Gamma (4.47)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Pulmonologist/ respiratory physician (subsequent)	£46.58	Gamma (4.66)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Other specialist visit	£37.67	Gamma (3.77)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Emergency room	£18.85	Gamma (1.89)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
CT scans	£28.83	Gamma (2.88)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
MRI	£22.37	Gamma (2.24)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET scans	£61.22	Gamma (6.12)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET-CT scans	£66.43	Gamma (6.64)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Ultrasound	£7.81	Gamma (0.78)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Nuclear medicine studies	£15.21	Gamma (1.52)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
DM1				
Hospitalisation	£171.19	Gamma (17.12)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Oncologist visits (subsequent)	£99.82	Gamma (9.98)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Surgeon visits	£36.28	Gamma (3.63)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Pulmonologist/ respiratory physician (subsequent)	£22.39	Gamma (2.24)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Other specialist visit	£24.48	Gamma (2.45)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Emergency room	£25.38	Gamma (2.54)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
CT scans	£37.68	Gamma (3.77)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
MRI	£33.56	Gamma (3.36)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET scans	£153.05	Gamma (15.31)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET-CT scans	£83.04	Gamma (8.30)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Ultrasound	£12.70	Gamma (1.27)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Nuclear medicine studies	£19.02	Gamma (1.90)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
DM2				
Hospitalisation	£171.19	Gamma (17.12)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Oncologist visits (subsequent)	£99.82	Gamma (9.98)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Surgeon visits	£36.28	Gamma (3.63)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Pulmonologist/ respiratory physician (subsequent)	£22.39	Gamma (2.24)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Other specialist visit	£24.48	Gamma (2.45)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Emergency room	£25.38	Gamma (2.54)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
CT scans	£37.68	Gamma (3.77)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
MRI	£33.56	Gamma (3.36)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET scans	£153.05	Gamma (15.31)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
PET-CT scans	£83.04	Gamma (8.30)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Ultrasound	£12.70	Gamma (1.27)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22
Nuclear medicine studies	£19.02	Gamma (1.90)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2021/22

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
CNS metastasis				
One-off radiotherapy	£18,616.13	Gamma (1,861.61)	B.3.5.3	NICE TA536; NHS Reference costs 2021/22
Cycle cost	£477.21	Gamma (47.72)	B.3.5.3	NHS Reference costs 2021/22; PSSRU 2022
End of life care				
Terminal care	£2,801.99	Gamma (280.20)	B.3.5.3	Brown et al.; NICE TA654; NHS Reference costs 2021/22; PSSRU 2010 and 2022

Abbreviations: AE, adverse event; CI, confidence interval; CNS, central nervous system; CT, computerised tomography; DF, disease free; DFS, disease-free survival; DM, distant metastasis; ECG, electrocardiogram; HCRU, healthcare resource use; KOL, key opinion leader; LRR, loco-regional recurrence; MRI, magnetic resonance imaging; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PDC, pemetrexed, cisplatin; PET, positron emission tomography; PSSRU, Personal Social Services Research Unit; SE, standard error.

B.3.6.2 *Assumptions*

Table 56 summarises the key model assumptions used in the model.

Table 56. Main model assumptions

Parameter/ Model setting	Assumption	Relevant section in submission
Survival outcomes from the ADAURA trial were extrapolated with an assumption of patients transitioning to cured if they remained in the disease free (DF) state.	When the extrapolated OS and DFS curves (aggregated from the model) were initially presented to clinical experts in 2020 (based on the January 17 2020 data cut—off), they found the long-term estimates were extremely pessimistic for this patient population compared to the outcomes observed in clinical practice, stating them to be more reflective of outcomes in the metastatic setting. To reflect the clinicians' expected clinical outcomes a structural cure assumption was implemented. Clinicians interviewed in both 2020 and 2023 agreed that patients who remained disease free at 5-years could be considered functionally cured. Following feedback from the EAG in TA761, cure for the osimertinib arm was implemented at year 8.[2] It is assumed that there is a gradual transition to cure in both arms. This gradual transition was assumed to take place over 1 year for the active surveillance arm (0% at year 4, 95% at year 5) and 4 years for the osimertinib arm (0% cure at 4 years, 95% at year 8). The assumption that 95% of patients would be cured if remaining DF is consistent with the preferred approach described in NICE technology appraisals in adjuvant, early-stage cancer (TA569, TA642, TA761).	B.3.3.3.1
Calibration factor	Whilst data from FLAURA was considered the most appropriate and clinically relevant data to inform the transitions in the distant metastatic states, the FLAURA population consists of stage IIIB/IV newly diagnosed metastatic patients which is distinctly different from ADAURA patients who have received radical treatment and progressed to metastatic disease. Both a literature search and interviews from clinicians confirmed that outcomes for patients with post-surgery recurrence compared to newly diagnosed stage IIIB/IV patients is expected to be different. Therefore, a calibration factor is calculated to align the OS extrapolations with the ADAURA OS KM, using the subsequent therapy settings per ADAURA trial. This calibration factor is applied to the post-DFS transitions (excluding the transitions modelled with GPM) and aligns the extrapolations with the observed overall survival.	B3.3.4
Survival outcomes from CancerLinQ were used to model the LRR health state, with a calibration HR of 0.765	Since in both the ADAURA and FLAURA trial there were not enough patients who progress from LRR to DM1 or from LRR to death, CancerLinQ was used instead. This US-registry is used to model the transitions from LRR to DM1 and death for both arms. The calibration HR accounts for the better efficacy of post-surgery patients vs newly diagnosed patients.	B.3.3.4, B.3.3.5
Survival outcomes from	Due to immature data from the ADAURA trial, survival data for the DM1 and DM2 health states were sourced from the	B.3.3.4, B.3.3.6

Parameter/ Model setting	Assumption	Relevant section in submission
the FLAURA trial were used to model DM1 and DM2 health states, with a calibration HR of 0.765	FLAURA trial of osimertinib in advanced EGFR+ NSCLC. Use of the FLAURA data was considered appropriate for modelling distant metastases by clinical experts.[37,46] However, this assumes equal efficacy for TKIs and PDC, therefore the efficacy of PDC is corrected using a HR from the NMA by Holleman et al. The calibration HR accounts for the better efficacy of post-surgery patients vs newly diagnosed patients.	
Clinical data for DM1 and DM2 health states	Due to immature data from the ADAURA trial, survival data for the DM1 and DM2 health states were sourced from the FLAURA trial of osimertinib in advanced EGFR+ NSCLC,[100] which formed the basis of TA654.[77] Use of the FLAURA data was considered appropriate for modelling distant metastases in the current model of resected metastatic NSCLC and also found to be generalisable to the UK population by six UK clinical experts.[46] Patients who are treated with PDC in DM1 receive Docetaxel in DM2, the other patients are treated with PDC in DM2. In both cases, 20% can be treated with the quad-regimen ABCP from the IMPower150 trial	B.3.3.6
DFS utility value	Similarly, DF utility score was estimated using data from the interim analysis of ADAURA; therefore, it may be subject to uncertainty due to data immaturity. However, it is difficult to validate the estimated utility value due to scarce availability of published HRQoL and cost-effectiveness studies in this patient population. Nafees et al, 2017,[156] reports the utility of NSCLC patients of all ages with stable disease and no adverse events is 0.84, [redacted] in the current model and offers some validation of the choice of utility value. To test uncertainty around the utility values, a scenario analysis was performed using the only published study with EQ-5D values (Andreas et al 2018).[21]	B.3.4.4
Utility values	Due to unavailability of an appropriate single source for health state utilities, values were obtained from different sources most relevant to the patient population and the health state considered in the model. Its impact on QALYs is subject to uncertainty. In addition, due to lack of published QoL data for patients in the LRR state, the HSUV for LRR was set equal to the HSUV for the DF state. To test uncertainty around the utility values, a scenario analysis was performed using the only published study with EQ-5D values (Andreas et al 2018).[21]	B.3.4.6
Treatment sequencing and retreatment with osimertinib	The impact of introducing osimertinib in resected stage IB-IIIA EGFRm NSLC on subsequent treatments (i.e. the rest of the treatment pathway) is unknown as the use of osimertinib in the adjuvant setting represents a step change in clinical practice. Clinicians have noted that retreatment with osimertinib in the metastatic setting is possible provided successful treatment was achieved in the adjuvant setting.	B.3.3.6

Parameter/ Model setting	Assumption	Relevant section in submission
	However, it is not possible to accurately predict what proportion of patients will be prescribed osimertinib for metastatic NSCLC in future clinical practice. Therefore, a conservative approach was applied in the model where 50% patients in the DM1 state were retreated at 4 years, and 50% were not. The uncertainty around both the percentage of patients retreated and the retreatment time point values were tested in the scenario analysis.	

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; HRQoL, health-related quality of life; HSUV, health state utility value; LRR, locoregional recurrence; NSCLC, non-small-cell lung cancer; OS, overall survival.

B.3.7 *Base-case results*

B.3.7.1 *Base-case incremental cost effectiveness analysis results*

Base case results are presented in Table 57. [redacted]. Osimertinib resulted in [redacted] additional QALYs compared with placebo (active monitoring), and incremental costs of [redacted], resulting in an ICER of £18,967 per QALY.

Table 57. Base-case results per patient

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG†	QALYs	Costs (£)	LYG†	QALYs	
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,967
Placebo (active monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-

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

B.3.7.2 *Clinical outcomes from the model*

A summary of clinical outcomes from the trial compared with the model is shown in Table 58.

Table 58. Summary of model results compared with clinical data

Outcome	Median survival (months) - Clinical trial result		Median survival (months) - Model result	
	Osimertinib	Placebo (active monitoring)	Osimertinib	Placebo (active monitoring)
DFS	65.8	28.1	72.0	29
OS	NR	NR	140.0	110.0

Abbreviations: DFS, disease-free survival; NR, not reached; OS, overall survival.
*Due to censoring/low number of patients at risk, and thus it is not representative of expected median OS

Additional clinical outcomes and disaggregated results for the base case analysis are presented in Appendix J.

B.3.8 *Sensitivity analyses*

B.3.8.1 *Probabilistic sensitivity analysis*

Probabilistic sensitivity analysis (PSA) was performed using 1,000 simulations to assess the uncertainty of the results by varying parameters simultaneously according to statistical distributions.

Results are presented in terms of cost-effectiveness planes and a cost-effectiveness acceptability curve (CEAC) to indicate the probability of each treatment being the most cost-effective at different willingness to pay thresholds.

B.3.8.1.1 Inputs

A summary of inputs and probability distributions used for the PSA is provided in Table 60. A full list of the inputs varied in the PSA, along with the 95% confidence intervals and statistical distribution, is provided in Appendix N.

Table 59. Summary of parameters included in the PSA

Category	Parameter	PSA distribution
Patient characteristics	BSA	Normal
Survival extrapolations	Survival model coefficients	Cholesky decomposition
HRQoL	Utilities	Beta
	AE disutilities	Beta
	Age-adjustment regression coefficients	Beta
AEs	Frequency of AEs	Beta
Costs	Acquisition costs	Gamma
	Administration costs	Gamma

Category	Parameter	PSA distribution
	Disease management costs	Gamma
	Terminal care costs	Gamma
	AE costs	Gamma
	EGFR testing costs	Gamma
	CNS metastasis costs	Gamma

Abbreviations: AE, adverse event; BSA, body surface area; CNS; central nervous system; EGFR, epidermal growth factor receptor; HRQoL, health-related quality of life; PSA, probabilistic sensitivity analysis.

B.3.8.1.2 Results

The cost-effectiveness plane from the PSA is shown in Figure 47, and illustrates the uncertainty around the incremental costs and QALYs in the model. The tabulated results are presented in Table 60.

Figure 47. Cost-effectiveness plane – Incremental PSA results (osimertinib vs placebo (active monitoring)

Abbreviations: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.
WTP threshold = £30,000 per QALY

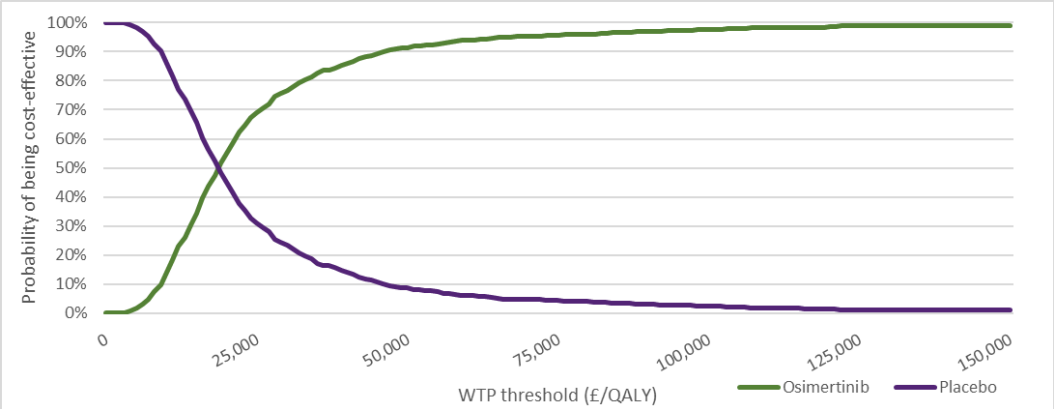
Table 60. Mean PSA results (reference case analysis) per patient

Treatment	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	18,378
Placebo (active monitoring)	[redacted]	[redacted]	[redacted]	[redacted]	

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

The cost-effectiveness acceptability curves for osimertinib and placebo (active monitoring) are displayed in **Figure 48**.

Figure 48. Cost-effectiveness acceptability curves (CEACs)



Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year; WTP, willingness-to-pay.

B.3.8.1.3 Discussion of variation between base case and PSA results

The average ICER resulting from the PSA was £18,378 per QALY compared to £18,967 per QALY in the deterministic base case analysis, with osimertinib reaching a 76.6% probability of cost-effectiveness for thresholds of £30,000 per QALY or greater.

B.3.8.2 *Deterministic sensitivity analysis*

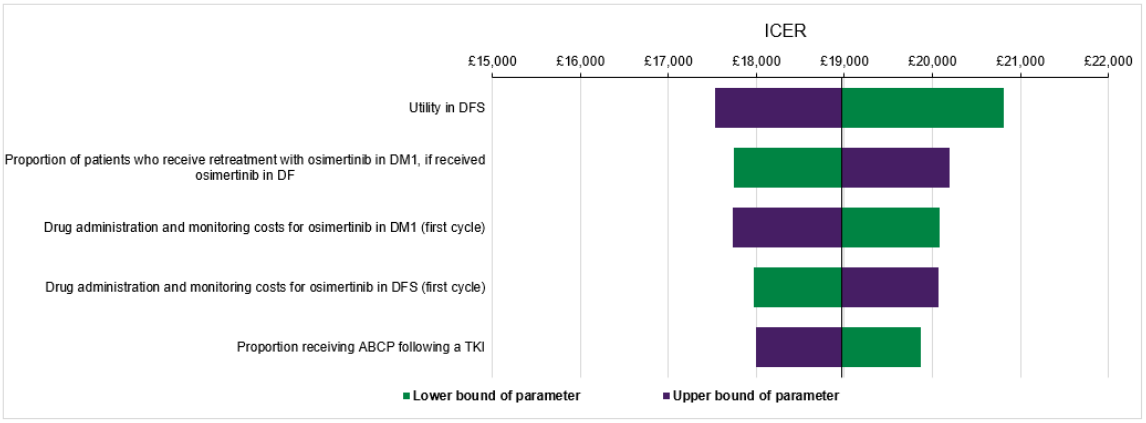
One-way deterministic sensitivity analysis (DSA) was performed to identify key model drivers. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available (e.g. for utilities), or using standard errors estimated based on ±10% variation around the mean where measures of variance around the base case values were not available.

A detailed list of parameters included in the DSA and their 95% confidence intervals are presented in Appendix N. Survival model parameters were excluded due to the covariance between these parameters, which were expected to provide misleading results when varying these estimates individually for the DSA.

B.3.8.2.1 Results

The results of the DSA are presented in the tornado diagram in **Figure 49**, which illustrates the key drivers of the model and their impact on the cost-effectiveness. The parameters where the difference in the ICER was ≥5% in either direction, along with their estimated ICERs, are shown in Table **61**.

Figure 49. DSA results – tornado diagram



Abbreviations: ABCP, atezolizumab plus bevacizumab in combination with carboplatin and paclitaxel, DFS, disease-free survival; DM, distant metastasis; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio

Table 61**. DSA results – key model drivers**

Parameter	Lower bound of parameter	Upper bound of parameter	Absolute difference
Utility in DFS	£20,805	£17,536	£3,269
Proportion of patients who receive retreatment with osimertinib in DM1, if received osimertinib in DF	£17,743	£20,192	£2,449
Drug administration and monitoring costs for osimertinib in DM1 (first cycle)	£20,085	£17,736	£2,348
Drug administration and monitoring costs for osimertinib in DFS (first cycle)	£17,965	£20,071	£2,106
Proportion receiving ABCP following a TKI	£19,862	£17,994	£1,869

Abbreviations: ABCP, atezolizumab plus bevacizumab in combination with carboplatin and paclitaxel; DF, disease free; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; PET, positron emission tomography; TKI, tyrosine kinase inhibitor.

The utility parameter had the greatest impact on the ICER, the top three being: the utility in DF, the proportion of patients who receive retreatment with osimertinib in DM1 (if received osimertinib in DF), and drug administration and monitoring costs in the first cycle for osimertinib in DM1. However, all of these parameters varied in the DSA resulted in an ICER less than £20,100 per QALY (i.e. highest ICER reached when decreasing the utility in the DF state).

B.3.8.3 *Scenario analysis*

The following scenario analyses were performed:

- Stereotactic radiotherapy 66%, 1 dose & Whole brain radiotherapy 34%, 2 doses (CNS metastasis in DM1)
- Waiting period before osimertinib retreatment, 42 months
- Waiting period before osimertinib retreatment, 60 months
- TP1 (DF to LR) distributions: Osimertinib, Weibull; Active monitoring, Generalized Gamma
- TP2 (DF to DM1) distributions: Osimertinib, Lognormal; Active monitoring, Generalized Gamma
- TP1: Osimertinib, Weibull; Active monitoring, Generalized Gamma & TP2: Osimertinib, Lognormal; Active monitoring, Generalized Gamma
- Osimertinib cure rate: timepoint after patients cured, 36 months; warm up period, 60 months
- QALY discount of 1.5% to cured patients

The results of the scenario analyses are presented in Table 62.

Table 62**.** Scenario analysis results per patient

Scenario	QALYs			Costs			ICER (£/QALY)
	Osimertinib	Placebo (active monitoring)	Incremental	Osimertinib	Placebo (active monitoring)	Incremental	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,967
Stereotactic radiotherapy 66%, 1 dose & Whole brain radiotherapy 34%, 2 doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,498
Waiting period before osimertinib retreatment, 42 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,199
Waiting period before osimertinib retreatment, 60 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,506
TP1 (DF to LR) distributions: Osimertinib, Weibull; Active monitoring, Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,710
TP2 (DF to DM1) distributions: Osimertinib, Lognormal; Active monitoring, Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,841
TP1: Osimertinib, Weibull; Active monitoring, Generalized Gamma & TP2: Osimertinib, Lognormal; Active monitoring, Generalized Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,010
Osimertinib cure rate: timepoint after patients cured,	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,405

Scenario	QALYs			Costs			ICER (£/QALY)
	Osimertinib	Placebo (active monitoring)	Incremental	Osimertinib	Placebo (active monitoring)	Incremental	
36 months; warm up period, 60 months							
QALY discount of 1.5% to cured patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,526
Mean health state utilities from Andreas et al, 2018, (DF=0.72; LRR=0.62; DM1 & DM2=0.67)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,926

Abbreviations: DF, disease free; DM, distant metastasis; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; QALY, quality-adjusted life year.

B.3.8.4 *Summary of sensitivity analyses results*

The scenarios that were most impactful on the results changed the ICER by:

- -39.9% (to £11,405) when altering the timepoint after which osimertinib patients are cured (36 months) and the warm up period (60 months)
- 30.3% (to £24,710) when the distributions in TP1 (DF to LR) were changed to Weibull and generalised gamma for the osimertinib and active monitoring arms, respectively.
- -18.1% (to £15,526) when a 1.5% QALY discount rate was applied to cured patients.

B.3.9 *Subgroup analysis*

From the ADAURA trial, data for two study populations were analysed. The primary study population as defined in the CSR was patients with stage II–IIIA disease. This represented a subset of the overall ADAURA study population, which included patients with stage IB–IIIA NSCLC. However, for the current submission, there are no subgroups within the population that should be considered separately. While the subgroup analysis of overall survival for subgroups according to stage (IB, II and IIIA) demonstrated the survival benefit was consistent across the subgroups, patients with stage IB disease comprise only 216 patients in total and only 40 events have occurred across both arms. Therefore, the subgroup analysis is not considered sufficiently robust for decision-making and this subgroup should not be considered separately.

B.3.10 *Validation*

B.3.10.1 *Validation of cost-effectiveness analysis*

Validation of the analysis was performed by two independent health economists. This included detailed checks of the technical design and implementation of the calculations, as well as logic and extreme value testing. Details of the validation process are provided in Appendix O (see separate Appendices document).

The general modelling approach and inputs were cross referenced with previous NICE technology appraisals of adjuvant treatments and subsequently validated by UK clinical experts to ensure that the model was reflective of clinical practice.

B.3.11 *Interpretation and conclusions of economic evidence*

Confidential commercial arrangements, including a patient access scheme (PAS) are available for osimertinib for treating EGFR T790M mutation-positive advanced NSCLC (TA653) and osimertinib for untreated EGFR mutation-positive NSCLC (TA654). A PAS price of [redacted].

The objective of the present analysis is to assess the cost-effectiveness of osimertinib when considered as an adjuvant treatment after complete tumour resection in adult patients with EGFR mutation-positive NSCLC. The cost-effectiveness analysis compared

osimertinib with placebo (active monitoring) and was conducted using a semi-Markov model with five health states and lifetime time horizon. The model was primarily based on data from ADAURA.

In the base case analysis, the use of osimertinib as an adjuvant treatment after complete tumour resection in adult patients with EGFR mutation-positive NSCLC produced considerable clinical and patient benefits compared to placebo (active monitoring), including [redacted] additional life years ([redacted]) and [redacted] additional discounted QALYs ([redacted]) per patient on average. With an incremental cost of £[redacted] this produced an ICER of £18,967 per QALY gained.

DSA indicated the model was robust, and that ICERs were stable and consistent with deterministic results, with ICERs below £20,100 per QALY in all one-way scenarios. The utility value in the DF state yielded the largest deviation from the base case, giving ICERs of £20,805 and £17,536 per QALY gained under the lower and upper bound values respectively.

PSA produced results consistent with the deterministic analysis with similar mean incremental costs and QALYs generated to the base case analysis, with 77% of all runs under the WTP threshold £30,000 per QALY gained. Cost-effectiveness acceptability curves demonstrated that the osimertinib arm had a high likelihood (76.6%) of being cost effective at the upper end of the conventional NICE threshold range of £30,000 per QALY gained.

Running the analysis under a range of key scenarios yielded similar results to the base case, with the highest ICER under any scenario – £24,710 per QALY gained – occurring when the parametric distributions for osimertinib and the active monitoring arm were Weibull and generalised gamma, respectively, for TP1 (DF to LR). Changing the timepoint after which osimertinib patients were cured to 36 months, after a 60-month warmup period, reduced the ICER to £11,405 per QALY gained.

Osimertinib is a highly efficacious, well-tolerated, and innovative treatment offering a potentially curative benefit and represents a paradigm shift to patients and healthcare providers, in a disease area with significant unmet need. Further to the important clinical benefits of osimertinib to patients, it is also a highly cost-effective treatment when compared against established clinical management reporting an ICER of £18,967 per QALY versus placebo (active monitoring), which is below the lower end of the conventional NICE threshold range of £20,000 per QALY.

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Single technology appraisal

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small cell lung cancer after complete tumour resection [ID5120]

Summary of Information for Patients (SIP)

January 2024

File name	Version	Contains confidential information	Date
ID5120_Osimertinib_SIP_10Jan24	1	No	10.01.24

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):

Generic name: Osimertinib Brand name: TAGRISSO®

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

Osimertinib is for people with early-stage non-small cell lung cancer (NSCLC) with specific changes (mutations) in the EGFR (epidermal growth factor receptor) gene (Ex19del or L858R mutation), whose cancer has been completely removed by surgery, and who may or may not have had chemotherapy following surgery (adjuvant chemotherapy).[1]

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.

In May 2021, the European Medicines Agency (EMA)[2] and the Medicines and Healthcare Regulatory Agency (MHRA)[3,4] granted marketing authorisation for osimertinib as a treatment for non-small cell lung cancer (NSCLC) after surgery to remove the cancer (for stage IB to IIIA lung cancer with an EGFR mutation). This is called adjuvant treatment. Osimertinib used after surgery and after optional adjuvant chemotherapy is considered an important and innovative breakthrough for people with NSCLC, and therefore osimertinib was granted marketing authorisation by the MHRA under Project Orbis, an initiative by the US Food and Drug Administration (FDA) Oncology Centre of Excellence (OCE), with a focus on high-impact cancer drugs.[5]

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 engages with the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information:

- EGFR Positive UK,
- Roy Castle Lung Cancer Foundation,
- Ruth Strauss Foundation,
- Asthma & Lung UK.

We are also corporate sponsors of UK Lung Cancer Coalition, which includes representation from patient groups but is not itself a patient group.
AstraZeneca UK publishes funding provided to UK patient groups on our website annually.
Since the most recent publication, a fair market value speaker payment was paid to EGFR Positive UK for speaking at an AstraZeneca UK-organised conference to provide patient insights to AstraZeneca staff.

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.

Overview of NSCLC

Lung cancer is the third most common cancer in the UK.[6] There are different types of lung cancer, divided into two main groups; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[7] NSCLC is the more common type of the two. Around 80 to 85 out of 100 lung cancers (80% to 85%) are NSCLC.[7]

Staging is a way of describing the size of a cancer and how far it has spread. There are four main stages of disease: stage I, stage II, stage III and stage IV.[8] Early-stage lung cancer typically refers to lung cancers that are stages I to III. Early-stage lung cancer is cancer that started in the lungs and has not spread to other parts of the body, such as the liver or brain.[8]

The symptoms of lung cancer often don't appear straight away and when they do appear, it can be hard to recognise them as a symptom of lung cancer as they can be wide-ranging and non-specific.[9,10]

People with lung cancer commonly develop a new cough or a persistent cough, they may cough up phlegm (sputum) with blood in it, become short of breath easily, feel an ache or pain in the chest or shoulder, or experience chest infections that keep coming back or a chest infection that doesn't get better.[11]

Other symptoms of lung cancer that are less common can include losing appetite, feeling tired all the time (fatigue), losing weight, developing swollen fingers and nails (also known as finger clubbing and is more common in NSCLC), or experiencing pain and swelling in joints (this condition is called hypertrophic pulmonary osteoarthropathy [HPOA]).[11]

How many people have the condition

NSCLC is the most common form of lung cancer in England and Wales.[7,12] Every year around 34,000 people are diagnosed with lung cancer in the UK.[13] Around 90% of lung cancer cases are NSCLC[6,7,12] and between 15 and 20% of patients will have surgery to remove the NSCLC.[13]

Life expectancy

People with early-stage NSCLC (stage I to III) can have treatments that will potentially cure them from their disease, and surgery to completely remove the tumour is the main treatment option.[14] For patients who have their cancer surgically removed, if the cancer doesn't come back within the first 5 years after surgery, the risk that it will come back later is very small.[15] In this case, these patients may be considered cured of their disease and are usually not scheduled for any further follow-up appointments.[15] However, for a small number of people (less than 3%) with NSCLC the cancer does come back more than 5 years after surgery.[16]

For people whose NSCLC comes back less than 5 years after surgery, the potential for a cure reduces.[14] People whose cancer has come back, either in the lungs where it started or spread to nearby lymph nodes, tissues, or organs, these patients can sometimes still have treatment with chemoradiotherapy (that is, having chemotherapy and radiotherapy together) with the goal of curing cancer. For patients whose cancer has come back and spread to more distant parts of the body (distant metastasis), there are limited curative treatments options available.[14,17-19] Therefore, the life expectancy of people whose cancer comes back after initial surgery gets shorter as the more extensively the cancer spreads throughout the body.[20,21] In England, the 5-year survival rate

(how many people are alive 5 years after they've been diagnosed or had surgery for lung cancer) for stage I, II, III, and IV lung cancers are 61%, 39%, 15%, and 4% (note, these rates are for all people with lung cancer, including those aged 75 years or older who typically have lower survival rates).[22] Overall, in the past 50 years in the UK, there have been limited improvements in lung cancer survival.[6]

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?

How lung cancer is diagnosed

Lung cancer is diagnosed using a variety of tests. These might include all or some of the following: chest X-rays, bronchoscopy, computerised tomography (CT), magnetic resonance imaging (MRI), positron-emission tomography CT (PET-CT), ultrasound scans, and lung cancer samples (biopsies).[14]

Testing for gene mutations in NSCLC

Some types of NSCLC have changes in particular genes and proteins.[23] These changes (mutations) make the cancer grow and divide at a different pace to normal cells, but these changes can also be used as targets for specific medicines.[23,24]

EGFR, or epidermal growth factor receptor, is a protein present on the surface of both healthy and cancer cells in the body.[23] EGFR regulates how cells grow and divide.[23] Sometimes this protein changes or mutates and becomes too active, which can lead to the formation of cancer, such as NSCLC. In patients with early-stage (IB-IIIA) NSCLC, EGFR mutations can be found in 8% to 16% of patients.[25,26]

Genetic testing for EGFR mutations is primarily done on tissue biopsies, small samples from the lung tumour usually taken when the patient was first diagnosed or from tissue removed during surgery. Genetic testing can also be done on patient blood samples if tissue samples are not available. EGFR mutation testing is done routinely in UK clinical practice for patients with NSCLC, including early-stage disease.[14,27]

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.

Unmet need

For people with early-stage NSCLC, surgery to completely remove the tumour is the main treatment for those who are fit enough to undergo such treatment.[14] However, despite the aim of providing a cure from the cancer through surgery, 44 - 76% of patients see the cancer return.[29]

In most cases when the cancer returns, it spreads to other organs outside of the lung (distant metastases) and when it does, there are no longer any treatments that can provide a cure.[17,30] For patients whose cancer spreads to other organs, people with NSCLC with an EGFR mutation are at a higher risk of their cancer spreading to the brain than people with NSCLC and no EGFR mutation.[31] The quality of life of patients worsens when the cancer comes back after surgery and the life expectancy is significantly reduced, especially for those whose cancer spread and develop brain tumours.[32,30,33,34]

There has long been a need for a treatment that can reduce the risk of NSCLC returning after the initial surgery to completely remove the tumour. The need for a treatment has been especially large for people with NSCLC with an EGFR mutation as this group of people are of higher risk of developing brain tumours.[31,35]

What treatments are currently used?

Once someone has received surgery for early-stage NSCLC, some people are offered chemotherapy to reduce the risk of the cancer coming back; this is called adjuvant chemotherapy.[14] However, adjuvant chemotherapy only offers quite small benefits in terms of prolonging the life expectancy of people with NSCLC; at 5 years after surgery, an additional 5% of patients are still alive if they received adjuvant chemotherapy compared with patients who only had surgery.[29,36] Also, not all patients can or want to have chemotherapy after surgery because it is associated with side effects, and patients may not be fit enough to have chemotherapy.[17] After surgery (with or without adjuvant chemotherapy), patients are followed up regularly over a period of 5 years to monitor for the cancer coming back.[15]

In January 2022, the National Institute for Health and Care Excellence (NICE) recommended that osimertinib should become available as a treatment option after surgery (with or without adjuvant chemotherapy) for people with early-stage NSCLC with an Ex19del or L858R EGFR mutation, while further data was collected.[37] Since then, osimertinib has become the standard treatment for patients with early-stage NSCLC with EGFR mutations.

The availability of osimertinib as a treatment for patients with early-stage, operable NSCLC with an EGFR mutation is an important step forward as there have been no medicines specifically for patients with early-stage NSCLC with EGFR mutations and no improvements in care after surgery for patients with NSCLC in the last 20 years.[14,37,38]

The aim of this health technology assessment is to assess adjuvant osimertinib for a routine funding recommendation based on assessment of the longer-term data that is now available.

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.

NSCLC can place a heavy physical and emotional burden on patients and their caregivers. Compared to the general population, people with NSCLC have both poorer physical health and poorer health-related quality of life.[39,40]

Although the number of disease symptoms that patients with early-stage NSCLC have after surgery to remove the tumour typically decreases, patients often experience lasting symptoms such as shortness of breath, tiredness, and poor mental health, with 20% of patients reporting clinically significant symptoms of anxiety and approximately 10% reporting depressive symptoms.[40-42] The quality of life of people with early-stage NSCLC can also be affected negatively by unfavourable and unintended signs or symptoms (adverse events) related to the surgery or post-surgical chemotherapy, and comorbidities such as congestive heart failure, chronic obstructive pulmonary disease, and coronary artery disease.[43]

For patients whose cancer comes back and spreads, despite initial surgery to remove the NSCLC, new tumours are often debilitating and lead to substantial clinical and quality of life burden that worsens as the disease progresses.[41,44] Brain tumours in particular, can have a large negative impact on a patient's quality of life; brain tumours are associated with seizures, problems with speech, vision, and memory, as well as fatigue, nausea, headaches, altered mental status, and mobility issues.[32] Additionally, patients who develop tumours in the brain are required to surrender their driving license, significantly limiting their independence and potentially placing additional burden on caregivers and other family members.

The worsened quality of life for patients whose disease comes back after surgery and spreads highlights the importance of lowering the risk of the disease coming back and preventing the cancer spreading.

The quality of life for the caregivers of patients with NSCLC is also negatively impacted. Caring for patients with lung cancer can be physically and psychologically burdensome, especially caring for patients with NSCLC that has come back after surgery and spread to other parts of the body as the patient's symptom burden increases and their function declines.[45]

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.

Osimertinib is a medicine that has already been approved by the EMA and MHRA for treating patients with EGFR mutation positive (with a mutation) NSCLC which has spread to other parts of the body (advanced or metastatic NSCLC).[2,3] Osimertinib has also been recognized as an innovative treatment when used to treat patients with early-stage, EGFR mutation positive NSCLC which has been removed by surgery. Osimertinib, as a treatment after surgery, was approved by the MHRA under Project Orbis in May 2021,[3,4] and by the EMA in May 2021.[2] Patients have been treated with osimertinib in the UK since it was made available through the Cancer Drugs Fund in January 2022,[37] and it has become the standard treatment for people after surgery of early-stage, EGFR mutation positive NSCLC.

Osimertinib is a targeted cancer growth blocker.[46] A targeted medicine is designed to target specific cells, for example cells with a mutation, while limiting damage to healthy parts of the body. Osimertinib works by blocking proteins called epidermal growth factor receptors (EGFR), a protein on the surface of cells, which helps the cells to grow and divide. Some cancer cells have a fault in the EGFR gene, which causes them to grow too much. Osimertinib blocks the signal from EGFR, and thereby stops the cancer cells growing.[47] Blocking EGFR may prevent the cancer from coming back after surgery to remove the tumour.[47]

Patients can be prescribed osimertinib by their doctor if their cancer contains faults in the EGFR gene, specifically a 'exon 19 deletion' or 'exon 21 substitution' mutation. If a test has shown that the cancer has these specific changes (mutations), the cancer is likely to respond to treatment with osimertinib.[47]

Before osimertinib was available, people with early-stage NSCLC who have received surgery to remove their tumour would be monitored regularly for their cancer coming back, and some patients would have chemotherapy after surgery; however, there were no targeted treatments available to prevent the cancer coming back, and chemotherapy only has limited benefits.[29,36,37] After surgery to remove NSCLC, patients would live with the distress and fear of the cancer coming back and the lack of an effective targeted treatment to lower that risk.[48]

The advantage to patients of receiving an innovative treatment, such as osimertinib, is that it provides significant clinical benefits as the treatment is tailored to treat their condition more effectively.[49-51]

3b) Combinations with other medicines

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

- Yes / 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 used 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 a tablet which is taken once a day. In England and Wales osimertinib can be taken for up to a maximum of 3 years, but may be stopped sooner, for example if the cancer returns, or if the patient experiences unacceptable side effects.[37] The recommended dose is one 80 mg tablet each day, but if necessary, your doctor may reduce the dose to one 40 mg tablet each day.[47]

Osimertinib should be taken at the same time each day, swallowed whole with a glass of water. It can be taken with or without food.[47]

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.

Osimertinib has been tested in the ADAURA trial, summarized in the table below. ADAURA is a clinical trial which evaluates the efficacy and safety of osimertinib (with or without prior chemotherapy) as an adjuvant therapy following complete resection in adult patients with stage IB–IIIA NSCLC with EGFR mutations.[49-51]

There are no other clinical trials of osimertinib as an adjuvant treatment after surgery in people with NSCLC.

Table 1: Clinical trials of adjuvant osimertinib in people with Stage IB-IIIA non-small cell lung cancer

Study name	NCT	Phase	Location	Population	Treatments studied	Number of patients	Expected completion date
ADAURA	NCT02511106	III	International	Stage IB-IIIA Non-small Cell Lung Cancer	Osimertinib 80 mg/ 40 mg	339	2030-12-31
					Placebo	343	

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 effectiveness and safety of osimertinib have been studied in a clinical trial called ADAURA. In the ADAURA trial, participants had early-stage EGFR-mutated NSCLC, which had been removed by surgery. Participants took either osimertinib or a placebo (a dummy drug with no active ingredient) after having their tumours removed by surgery. Post-surgery chemotherapy was allowed prior to osimertinib, but this was not compulsory (this was decided by the participant and their doctor).[23]

The clinical trial recruited 682 adults who were randomly assigned to take either osimertinib or a placebo; 339 were treated with osimertinib and 343 were given placebo (no active medicine).[23] Neither the participant nor their doctor knew which treatment they were taking. The treatment was given for 3 years or until their cancer returned, or until the participant decided to stop treatment for other reasons.[52]

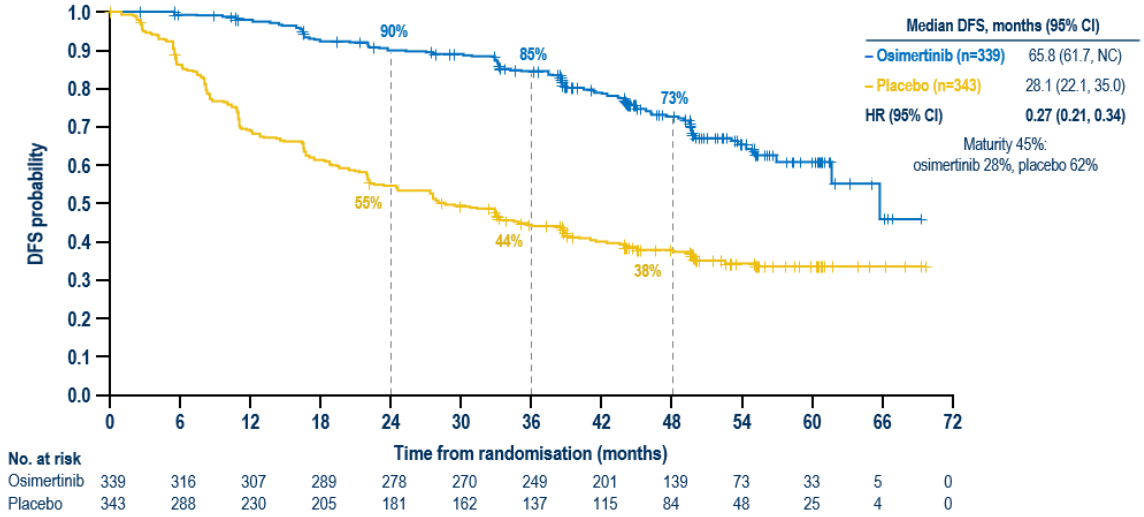
The primary aim of the ADAURA clinical study was to see how long participants in the study with early-stage EGFR-mutated NSCLC would remain alive and cancer-free with osimertinib treatment (known as disease-free survival), after having their tumours completely removed by surgery.[23,52] A secondary goal of the trial was to measure the impact of osimertinib on overall survival (OS), which is the length of time people are alive after initially receiving treatment.[52]

Primary outcome: Disease-free survival (Document B: B.2.6.1.1)

Patients who took osimertinib stayed cancer-free for longer, regardless of whether they received chemotherapy after surgery. Adults taking osimertinib were 73% less likely to have their cancer come back or die compared with those who took no active medicine. At 4 years, 73% of people given osimertinib didn't have their cancer come back and were still alive compared to 38% of people given no active medicine.

A Kaplan-Meier (KM) plot shows the rate at which an event, in this case the return of NSCLC or death, occurs over time. A steeper slope indicates a higher event rate and therefore a worse prognosis. The KM plot in Figure 1 below shows a clear and sustained separation of the curves for osimertinib and placebo, which means that a greater number of participants taking osimertinib remained alive and cancer-free for a longer time compared with those who were given placebo.

Figure 1. Kaplan-Meier plot of DFS in ADAURA – final analysis for the overall population

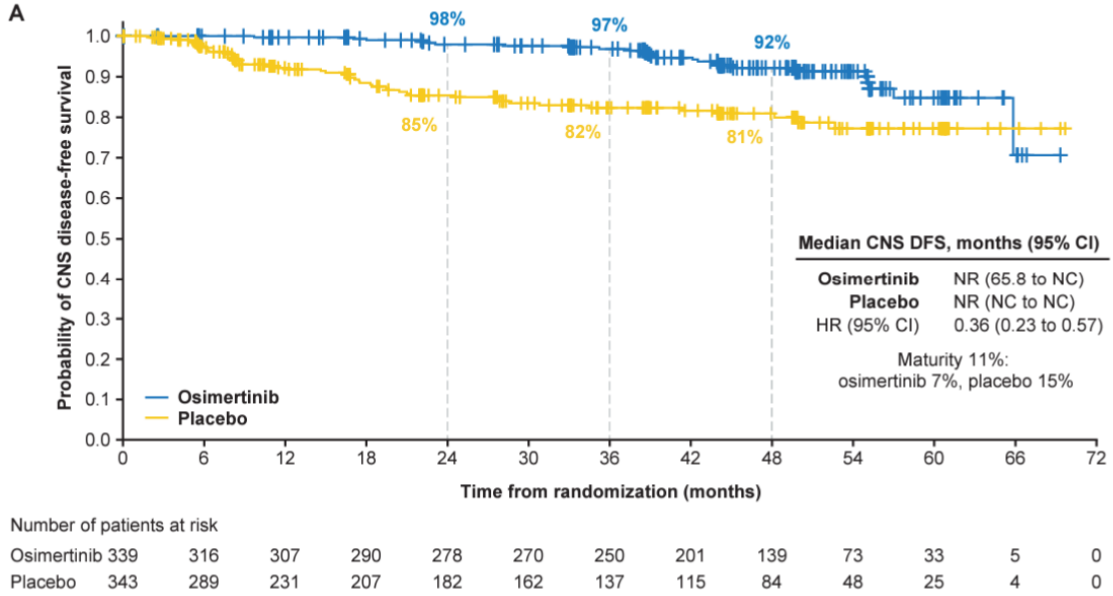


Notes: Median follow-up for osimertinib was 44.2 months (range 0 to 69) and for placebo was 27.7 months (range 0 to 70); DFS by investigator assessment; Tick marks indicate censored data; HR<1 favours osimertinib.
Abbreviations: CI, confidence interval; DFS, disease-free survival; NC, not calculated.
Sources: Herbst et al. 2023[50]; Tsuboi 2022[53]

Secondary outcome: Central nervous system disease-free survival (Document B: B.2.6.1.2)

In the ADAURA trial, osimertinib treatment reduced the risk of tumours spreading to the brain and spinal cord, that is, the central nervous system (CNS), by 64% compared with placebo (Figure 2).

Figure 2. Kaplan-Meier plot of CNS DFS in ADAURA study; overall population, post hoc updated analysis

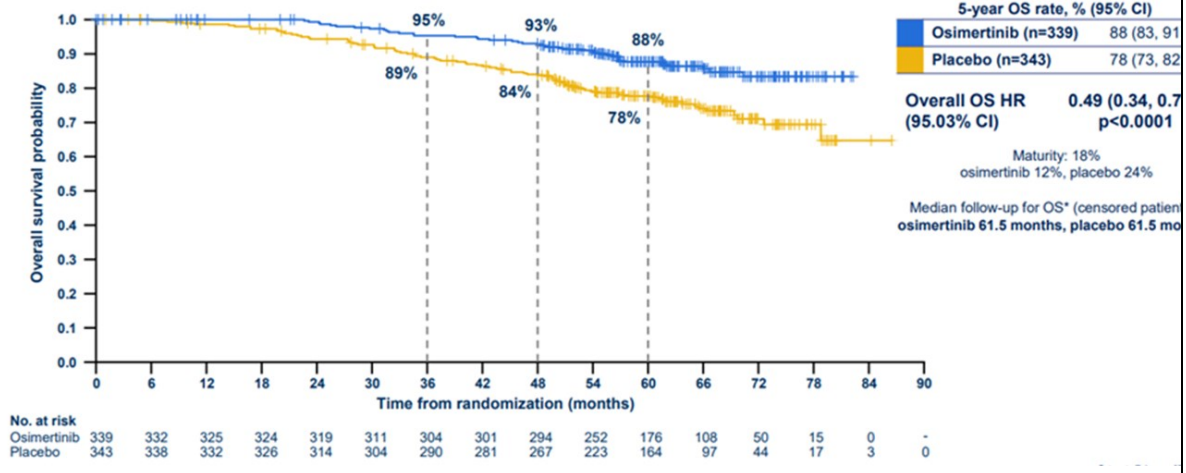


Abbreviations: CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; NC, not calculable; NR, not reached.
Source: Herbst et al, 2023[54]

Secondary outcome: Overall survival (Document B: B.2.6.1.2)

Patients who were treated with osimertinib in ADAURA lived longer than patients who didn't have osimertinib after surgery of NSCLC (Figure 3). At 5 years, 88% of patients given osimertinib were still alive compared with 78% of people given no active medicine.

Figure 3. Kaplan-Meier plot of OS in ADAURA –final OS analysis in the overall population



Notes: DCO 27 January 2023.
Tick marks indicate censored data; Alpha allocation of 0.0497.
*Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.
Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival.
Sources: Tsuboi et al, 2023[51]; Herbst et al. 2023[54]

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.

In the ADAURA trial patients' quality of life was measured using a generic questionnaire rather than a lung cancer-specific questionnaire. The rationale for this was that patients in ADUARA, who have no evidence of disease after surgery, predominantly don't have any symptoms and the different aspects of physical and mental health of these patients are better captured with a generic quality of life questionnaire.[55]

The ADAURA trial showed that patients' health-related quality of life during the 3 years of treatment was similar between those patients receiving osimertinib and those receiving placebo.[56] Taking osimertinib after surgery of NSCLC did not have a negative impact on people's quality of life.[56]

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 any medicine, this medicine can cause side effects, although not everybody gets them. How often and how severe the side effects (or 'adverse events') are can vary from person to person. In the ADAURA trial osimertinib was generally well tolerated.[50] Side effects can be managed by reducing the dose or by stopping osimertinib for a period of time.[1] The number of patients who stopped osimertinib treatment, had a dose reduction or treatment interruption because of a side effect, were relatively low in the ADAURA trial.[50] The most commonly reported side effects with osimertinib included diarrhoea, paronychia, dry skin, pruritis, and cough (Table 2).[50]

Table 2: Most common adverse events (≥20% of patients in either treatment group) in ADAURA

Side effect	Symptoms	Osimertinib % of patients	Placebo % of patients
Diarrhoea	Passing of loose or watery stools more than three times a day	47%	20%
Paronychia	An infection of the skin around a fingernail or toenail that can become swollen, red, and painful, and a pus-filled blister (abscess) may form.	27%	1%
Dry skin	Skin roughness, tightness, flaking, and scaling	25%	7%
Pruritis	Severely itchy skin	21%	9%
Cough	Reflex reaction to clear the airways	20%	18%

Sources: Herbst et al, 2023[54]; Tsuboi et al, 2023[51]

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
-

The key benefits of osimertinib to patients with early-stage EGFR-mutated NSCLC removed by surgery, their families, caregivers and society include:

- Patients who take osimertinib stay cancer-free for longer, regardless of whether they also received chemotherapy after surgery.[50]
- Osimertinib treatment reduced the risk of tumours spreading to the brain and spinal cord, that is, the central nervous system.[50]

- Patients who are treated with osimertinib live longer than patients who don't have osimertinib after surgery of NSCLC.[51]
- The side effects experienced by the patients taking osimertinib are usually well managed and they are consistent with what is expected for this medicine.[50,51]
- Taking osimertinib after surgery of NSCLC does not have a negative impact on people's quality of life during the time they receive adjuvant osimertinib.[56]
- Although these were not studied in the ADAURA trial, it is anticipated the quality of life of the families and caregivers of patients who are treated with osimertinib is likely to be maintained as their loved ones stay cancer-free for longer, thereby avoiding the physical and emotional burden of caring for someone whose cancer has come back and spread.[45,50]

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

Like any medicine, osimertinib can cause side effects. As the alternative to osimertinib treatment for EGFR mutated early-stage NSCLC after surgery completely removing the tumour, is active monitoring for the cancer to return, that is, no treatment (with or without adjuvant chemotherapy), a disadvantage of osimertinib compared with active monitoring is potential side effects. However, based on the results from the ADAURA trial, osimertinib is generally well tolerated.[50]

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.

Five different health states are used to model the different stages of NSCLC. Patients start in the disease-free (DF) health state after surgery and stay there unless the cancer returns or they die. If the cancer returns, this can be local (modelled as a locoregional recurrence, LRR) or metastatic (modelled as first-line distant metastasis) which are modelled as separate health states. Metastatic patients can receive multiple lines of treatment, therefore the model has separate health states for first-line and second-line treatments for metastatic patients . The final health state is death, where every modelled patient ends, either due to death caused by NSCLC or natural causes.

Osimertinib is given after tumour resection, with the aim to reduce the chance the cancer comes back. Since this allows more patients to stay free of NSCLC after resection, osimertinib is expected to extend life.

The economic model uses data from the ADAURA study of osimertinib vs placebo to determine the likelihood of leaving the DF health state. When the cancer returns locally, patients are in the LRR health state. The likelihood of leaving this health state is based upon data from the CancerLinQ database (a US-based real-world registry). Finally, for the metastatic health state, data from the FLAURA study was used (the key trial for osimertinib in the metastatic setting of NSCLC).[57] The model also included a function that patients may be considered to be functionally cured if they have not experienced recurrence after being treatment free for 5-years in the placebo arm and 8-years in the osimertinib arm.[15]

To model a patient's transition between health states, survival data from the above studies were used. However, since data from the studies is only available for the first years, the model uses mathematical functions to predict how the disease behaves over a longer time period. This was done following the standard practice and guidance from the NICE decision support unit (DSU).[58]

The quality of life is modelled using the different disease stages as described above. The quality of life is the highest in the DF and LRR health states, becomes worse after the cancer becomes metastatic, and is worst for patients receiving 2nd line metastatic treatment. Because osimertinib keeps more patients alive and disease-free, osimertinib improves the quality of life.

Quality of life was measured using a questionnaire consisting out of 36 questions (SF-36) and looks at different elements of wellbeing, varying from physical functioning to pain to mental health) in the ADAURA studies. A similar questionnaire was used (EORTC QLQ-LC13) in the FLAURA study, which is more specific for cancer patients. The FLAURA study is a phase 3 trial comparing osimertinib with first-generation EGFR-TKIs (gefitinib or erlotinib) in patients with untreated, advanced/metastatic NSCLC not amenable to surgery/radiotherapy.

The current treatment for NSCLC patients after resection, is active monitoring. Since there are no drug costs for active monitoring, the drug costs increase when using osimertinib.

However, the use of health services (for example, number of days in the hospital, MRI or PET scan) is lower; the use of health services becomes more when the disease becomes more severe, this is also how the model works; there is more use of the health services in the metastatic health states than in the DF health state (when patients are disease-free after surgery). Within a health state, the same use of the health services is assumed between osimertinib and placebo. Since

osimertinib patients generally stay in better health, the use of health services is lower compared to the placebo patients.

The model uses data from the ADAURA and FLAURA studies, which only have data available for the first years of the disease. Therefore, the model needed to make assumptions over how the disease behaves over a lifetime. Different mathematical functions to estimate this were used and tested as scenarios. These scenarios showed that the impact on the outcomes (measured as cost-effectiveness values (ICERs)) was minor, as all scenarios fell within the conventional NICE willingness-to-pay (WTP) threshold range of £20,000–£30,000 per quality adjusted life years (QALY).
Another uncertainty is the quality of life in the DF health state. This had the largest effect on the ICER (+/- 8%).

The model shows that osimertinib improves the overall survival with 2.08 years (from 12.59 years to 14.67 years). Also, the quality of life improved with 1.05 quality adjusted life years (QALY) (from 7.1 QALY to 8.15 QALY). Osimertinib is more expensive than active monitoring, and combined with the increased quality of life, an incremental cost effectiveness ratio can be calculated. The model shows that osimertinib comes with a cost of £23,366 per QALY gained. This is below the threshold of £30,000 set by NICE.

Based on the evidence available and the company's economic analysis, osimertinib would be considered as offering a good use of NHS resources, as a new treatment for patients with EGFR mutated, early-stage NSCLC that has been removed by surgery. This will be re-assessed by NICE in this appraisal and their decision will be based on the latest available data for osimertinib in this setting.

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)

There has long been a need for a treatment that can reduce the risk of NSCLC returning after the initial surgery to completely remove the tumour. The need for a treatment has been especially large for people with NSCLC with an EGFR mutation as this group of people are of higher risk of developing brain tumours.[31,35] The introduction of adjuvant osimertinib, which is the first targeted adjuvant therapy for this patient group, has provided a step change in the treatment of early-stage NSCLC after surgery, and is now considered standard of care for patients with early-stage, EGFR-mutated NSCLC after surgery.[38]

The results of the ADUARA trial clearly demonstrate that adjuvant osimertinib is a highly innovative treatment;

- Patients who take osimertinib stay cancer-free for longer, regardless of whether they also received chemotherapy after surgery.[50]

- Osimertinib treatment reduced the risk of tumours spreading to the brain and spinal cord.[50]
- Patients who are treated with osimertinib live longer than patients who don't have osimertinib after surgery of NSCLC.[51]

Osimertinib is thereby reducing the burden on patients as well as the healthcare system.[50,51]

Based on the ADUAURA trial, regulatory agencies that evaluates and approves new medicines, have recognised adjuvant osimertinib as an innovative treatment:

Adjuvant osimertinib was granted FDA breakthrough therapy and was approved for use in the US under Project Orbis in December 2020.[59] Further, osimertinib was the first medicine granted marketing authorisation by the MHRA in the UK within Project Orbis in May 2021.[4] Project Orbis is an FDA OCE initiative, with a focus on high-impact cancer drugs.[5]

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
No equality issues are anticipated.

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.
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

Patient groups and charities:

- EGFR+UK

Further information about osimertinib:

- TAGRISSO®

4b) Glossary of terms

Adjuvant: Treatment offered after surgery to reduce the chance of cancer coming back by destroying any remaining cancer cells.
Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe.
Biopsy: A process in which a very small part of tissue in the body is removed to look for signs of disease.
Clinical trial/clinical study: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study. When it is called "phase III clinical trial" it tests the safety and how well a new treatment works compared with a standard treatment. For example which group of patients has better survival rates or fewer side effects. In most cases, treatments move into phase III clinical trials only after they meet the goals of phase I and phase II clinical trials. Phase 3 clinical trials may include hundreds of people.
CNS: Central nervous system
CT scan / computerized axial tomography scan: A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3-D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly. A computerized axial tomography scan may be used to help diagnose disease, plan treatment, or find out how well treatment is working. Also called CAT scan, computed tomography scan, computerized tomography, and CT scan.
Curative: a treatment approach given to a person that aims to completely destroy or get rid of all cancer cells in the body
DFS: Disease-free survival, how long people with cancer would remain tumour-free
EGFR: Epidermal growth-factor receptor, a protein on the surface of cells in the human body
EMA: European Medicines Agency: The regulatory body that evaluates, approves, and supervises medicines throughout the European Union
FDA: Food and Drug Administration: The regulatory body that evaluates, approves, and supervises medicines in the USA
HTA: Health Technology Assessment (bodies): Bodies that make recommendations groups regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

Lymph nodes: the lymph nodes are small glands that are part of the body's lymphatic system that carries immune cells that help fight infections or cancer cells. Cancer cells can either start in lymph nodes or spread to the nodes from elsewhere in the body, e.g., the lungs
MHRA: Medicines and Healthcare Products Regulatory Agency: The regulatory body that evaluates and approves medicines in the UK
MRI: A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. MRI makes better images of organs and soft tissue than other scanning techniques, such as computed tomography (CT) or x-ray. MRI is especially useful for imaging the brain, the spine, the soft tissue of joints, and the inside of bones. Also called magnetic resonance imaging, NMRI, and nuclear magnetic resonance imaging
NSCLC: Non-small cell lung cancer
OS: Overall survival, how long people with a disease live
PET-CT: Positron emission tomography computed tomography
Placebo: A dummy drug with no active ingredient
Quality of life: The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and ability to carry out activities of daily living
Stage: A description of how severe a disease is.
Targeted therapy: A targeted therapy is a type of cancer treatment that targets specific proteins that control how cancer cells grow, divide, and spread.
Treatment that has been designed to fix specific unhealthy areas in the body, such as cells with a specific mutation, for example an EGFR mutation, while limiting damage to healthy parts of the body.
X-ray imaging: A procedure that uses a type of high-energy radiation called x-rays to take pictures of areas inside the body. X-rays pass through the body onto film or a computer, where the pictures are made. The tissues and organs usually appear in various shades of black and white because different tissues allow different amounts of the x-ray beams to pass through them. X-ray imaging is used to help diagnose disease and plan treatment. Also called radiography.

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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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (review of TA761) [ID5120]

Clarification questions

25/01/2024

File name	Version	Contains confidential information	Date
ID5120_Osimertinib_Clarification questions response_[CIC redacted]_12Jan24	1	Yes	12 Jan 24

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 search strategy

A1. Company's submission (CS) Appendices, Section D.1.1, page 13. The text states that searches were conducted of the WHO International Clinical Trials Registry Platform (ICTRP). Was ClinicalTrials.gov also searched?

Response:

ClinicalTrials.gov was not searched separately but it was included by searching Cochrane Central Register of Controlled Trials (CENTRAL). CENTRAL includes bibliographic databases from published and unpublished sources including ClinicalTrials.gov.

A2. CS Appendices, Section D.1.1.1.1, page 14. The text states that the terms used to search for randomised controlled trials (RCTs) and other eligible study types were "adapted from validated filters from the Scottish Intercollegiate Guidelines Network." Whilst the EAG is familiar with SIGN and its work, it is unaware of their filters having undergone any formal validation. Please provide citations to the relevant validation studies along with details of any alterations you have made to the published versions.

Response

Searches were based on internationally recognised guidelines, including the Scottish Intercollegiate Guidelines Network (SIGN). As per the SIGN website "search filters are pre-tested strategies that identify the higher quality evidence from the vast amounts of literature indexed in the major medical databases. Filters exist for most types of experimental design, and are comprised of index terms relating to study type and specific terms associated with the methodological description of good experimental design." SIGN filters are widely used in search strategies, including for HTA, and are publicly available. The systematic literature review (SLR) included other methods to ensure that no relevant report was missed by checking the bibliography list of other SLRs.

Details of the alterations to the search are displayed below and were modified to, in most cases increase the sensitivity of the search; terms in green were additional terms added; terms in red were not included; and in orange were any other modifications.

Embase <1974 to 2023 October 13>	
1	exp non small cell lung cancer/
2	NSCLC.ti,ab,kw.
3	1 or 2
4	exp lung tumor/
5	((lung or pulmonary) adj3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno* or squamous)).ti,ab,kw.
6	4 or 5
7	(non small or nonsmall).ti,ab,kw.
8	6 and 7
9	3 or 8
10	((early* adj2 cancer) or early stage or locally advanc* or stage 1b or stage Ib or stage 2a or stage IIa or stage 2b or stage IIb or stage 3a or stage IIIa or stage Ib-IIIa or stage 1b-3a).ab,ti,kw.
11	9 and 10
12	exp epidermal growth factor receptor/
13	("epidermal growth factor receptor" or "epithelial growth factor receptor" or EGFR* or erb*).ti,ab,kw.
14	12 or 13
15	exp programmed death 1 ligand 1/
16	("programmed death ligand 1" or "PD L1" or PDL1 or "cluster of differentiation 274" or CD274 or "CD 274" or "B7 homolog 1" or "B7 H1" or B7H1).ti,ab,kw.
17	15 or 16
18	randomized controlled trial (topic)/
19	randomized controlled trial/
20	clinical trial/
21	clinical study/
22	controlled clinical trial/

23	multicenter study/
24	exp randomization/
25	single blind procedure/
26	double blind procedure/
27	crossover procedure/
28	placebo/
29	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
30	(phase 2* or phase II* or phase 3* or phase III* or phase 4* or phase IV*).tw.
31	(clinical adj trial*).tw.
32	((singl* or doubl* or treb* or tripl*) adj (blind*3 or mask*3)).tw.
33	placebo*.tw.
34	(allocat* adj2 random*).tw.
35	randomi?ed controlled trial*.tw.
36	rct.tw.
37	(Trial or study).ti.
38	((single arm or single-arm) adj3 (study or studies or trial*)).tw.
39	(Open-label adj3 (trial* or stud*)).tw.
40	((Non-blinded or unblinded) adj3 (stud* or trial*)).tw.
41	or/18-40
42	exp Cohort Analysis/
43	cohort analy*.tw.
44	(cohort adj (study or studies)).tw.
45	exp longitudinal study/
46	Longitudinal.tw.
47	exp Follow Up/
48	(follow up adj (study or studies)).tw.
49	exp prospective study/
50	(Prospective adj (study or studies)).tw.
51	(evaluation adj (study or studies)).tw.
52	exp retrospective study/
53	retrospective*.ti,ab.
54	(chart adj3 review).tw.
55	exp observational study/
56	(observational adj (study or studies)).tw.
57	Case control.tw.
58	Cross sectional.tw.
59	exp cross-sectional study/
60	or/42-59
61	("conference abstract" or "conference review").pt.
62	limit 61 to yr="1974-2017"
63	exp animals/ not exp humans/
64	(comment or editorial or "case reports").pt.
65	(case stud* or case report*).ti.
66	historical article/
67	case study/

68	or/62-67
69	11 and 41
70	11 and (14 or 17)
71	70 and 60
72	69 or 71
73	72 not 68
74	limit 73 to yr="2020 -Current"

SIGN filter	
Randomised controlled studies	
1	Clinical Trial/ (505836)
2	Randomized Controlled Trial/ (430740)
3	controlled clinical trial/ (91696)
4	multicenter study/ (211094)
5	Phase 3 clinical trial/ (0)
6	Phase 4 clinical trial/ (0)
7	exp RANDOMIZATION/ (88833)
8	Single Blind Procedure/ (0)
9	Double Blind Procedure/ (0)
10	Crossover Procedure/ (0)
11	PLACEBO/ (0)
12	randomi?ed controlled trial$.tw. (118033)
13	rct.tw. (13355)
14	(random$ adj2 allocat$).tw. (26671)
15	single blind$.tw. (14081)
16	double blind$.tw. (131298)
17	((treble or triple) adj blind$).tw. (496)
18	placebo$.tw. (184669)
19	Prospective Study/ (431057)
20	or/1-19 (1362945)
21	Case Study/ (1825273)
22	case report.tw. (246534)
23	abstract report/ or letter/ (941014)
24	Conference proceeding.pt. (0)
25	Conference abstract.pt. (0)
26	Editorial.pt. (418735)
27	Letter.pt. (941014)
28	Note.pt. (0)
29	or/21-28 (3053616)
30	20 not 29 (1330027)
Observational studies	
1 Clinical study/	
2 Case control study	

3 Family study/
4 Longitudinal study/
5 Retrospective study/
6 Prospective study/
7 Randomized controlled trials/
8 6 not 7
9 Cohort analysis/
10 (Cohort adj (study or studies)).mp.
11 (Case control adj (study or studies)).tw.
12 (follow up adj (study or studies)).tw.
13 (observational adj (study or studies)).tw.
14 (epidemiologic$ adj (study or studies)).tw.
15 (cross sectional adj (study or studies)).tw.
16 Or/1-5,8-15

A3. PRIORITY. CS Appendices G, H, and I. The searches reproduce the original database searches from 2020 but not those from 2023. Please provide a full transcript of these update searches (including numbers of results retrieved) and show how these were backdated to 2020.

Response:

All documentation of the 2023 searches are provided as separate files (including numbers of results retrieved). All records from 2020 were included in the update searches to allow an overlap in records from the bibliographic databases between the original and update search.

A4. CS Appendices G, H, and I, search strategies. The population string for the economic, utility and cost and resource use searches only includes the US spelling of “tumor” (whereas the clinical searches included a wildcard to allow for the UK spelling). Please comment on the possible implications for retrieval.

Response:

For the economic, utility and cost and resource searches, “tumor” is used as a subject heading (lung tumor/). The search strategy for economic, utility and cost and resource use is based on broad terms as it only includes terms for tumour site (lung or pulmonary or bronchus or bronchogenic or bronchial or bronchoalveolar or alveolar), combined with terms for non-small cell lung cancer. The search strategy

did not combine with tumor as a text term. The impact on retrieval of relevant information is therefore likely to be minimal.

A5. CS Appendix G.1.1, page 120. The text states that the Cochrane Library searches included DARE, NHS EED and the HTA database. However, these sources are no longer hosted by Cochrane. Please confirm if they were searched in their new locations (CRD and INAHTA, respectively).

Response:

Both DARE and NHS EED are no longer receiving new records. New records were added to the DARE database up until March 2015 and to NHS EED until March 2018. As the original search was conducted in 2020, DARE and NHS EED were included in the SLR search strategy for completeness. Including those databases in the SLR update, which was completed in December 2023, would not contribute to generating new results. Thus, these databases were replaced with searches of INAHTA and the CEA registry in order to capture a wider range of ongoing and published HTAs.

A6. CS Appendix G.1.1, page 120. According to the text, the proceedings of the European Lung Cancer Congress were searched in 2020 but not in the 2023 update. Was there a reason for this omission?

Response:

In the SLR update, conference proceedings (including European Lung Cancer Congress) were captured within the Ovid search. In the original search in 2020, relevant conference proceedings were likely to be captured in the main data base search, which was run through Embase, but for completeness conference proceedings were also searched separately.

A7. CS Appendix G.1.2, page 121. The text reports that in 2020 there was supplementary hand searching of reference lists of included studies and systematic reviews, plus a number of websites. Why were these not searched again in 2023?

Response:

The SLR update did not include hand searching for the grey literature, the search strategy/terms were largely improved compared to how it was done in the original

SLR. In addition, the original protocol did not initially incorporate hand-search; however, it was conducted subsequently upon reviewing publications retrieved from the search, given the limited information available on adjuvant osimertinib at that time. Due to the combination of improved search terms, increase in literature now available in this setting and the inclusion of a wider selection of databases (this time through OVID), a hand search was not performed for the SLR update.

Section B: Clarification on clinical effectiveness data

Comparators

B1. PRIORITY. CS, Section B.1.1, page 11. The text argues that adjuvant chemotherapy is not a relevant comparator for osimertinib. One of the arguments made in the CS is that "Adjuvant osimertinib is not intended or expected to displace adjuvant chemotherapy as it represents an additional adjuvant treatment option." In ADAURA, approximately 60% of patients had received prior chemotherapy, whereas the Systemic Anti-Cancer Therapy (SACT) data (CS, Appendix R) suggest that only around 27% of osimertinib-treated patients had received prior adjuvant chemotherapy. The stage distributions in ADAURA and SACT appear to be broadly similar. This might suggest that adjuvant chemotherapy is being displaced as patients are receiving osimertinib directly after surgery without prior chemotherapy. Please comment on this. Please also comment on whether data exist to perform an indirect comparison between adjuvant osimertinib (with or without prior adjuvant chemotherapy) versus adjuvant chemotherapy alone.

Response:

While there is less use of adjuvant chemotherapy in the SACT population (27%) compared to the ADAURA trial (60%), there is paucity of evidence regarding the rate of adjuvant chemotherapy in the population of interest in UK clinical practice prior to the introduction of osimertinib. Therefore, the suggestion that adjuvant chemotherapy is being displaced by adjuvant osimertinib cannot be substantiated.

Regarding the feasibility of an indirect comparison, it should be noted that the decision to give adjuvant chemotherapy and adjuvant osimertinib are two separate and sequential treatment decisions. Therefore, to compare adjuvant chemotherapy

with adjuvant osimertinib, costs and outcomes would need to be collected from the point of decision to treat/ not to treat with adjuvant chemotherapy. The randomisation point in the ADAURA trial was at the point of decision to treat with osimertinib, i.e., after the adjuvant chemotherapy decision. Therefore, the costs and outcomes for the period of time while patients are receiving adjuvant chemotherapy is not captured in the ADAURA trial, meaning outcomes for any patients who do not successfully complete adjuvant chemotherapy or who experience disease recurrence whilst taking chemotherapy are not captured. As such, the ADAURA data is not appropriate for use in an ITC with adjuvant chemotherapy due to the later randomisation point.

Adjuvant chemotherapy has been long established to offer minimal survival benefits (CS pg. 24 “However, adjuvant chemotherapy offers only modest benefits to patients; the risk of disease recurrence or death has been shown to be reduced by 16% versus no chemotherapy (HR: 0.84; p<0.001), and the 5-year absolute survival benefit of adjuvant chemotherapy is around 5% for stage IB to stage III disease)[1,2] and has never undergone a HTA to establish if it’s use is a cost-effective use of NHS resources. The ANITA study demonstrated there was no survival benefit for patients with IB disease who received adjuvant chemotherapy following resection compared to patients who did not receive adjuvant chemotherapy following resection (HR: 1.10, 95% CI: 0.76-1.57) whereas the ADAURA trial demonstrated DFS and OS benefits for the IB subgroup.[3-5] It should also be noted that the ADAURA data demonstrates the treatment effect of osimertinib is consistent regardless of prior adjuvant chemotherapy use (CS figure 8 and figure 13).

Clinical effectiveness evidence for osimertinib

B2. PRIORITY. CS, Section B.2, page 31. The long-term benefit of adjuvant osimertinib on disease-free survival (DFS) was noted as a key area of uncertainty in NICE Technology Appraisal (TA) 761. The most recent data from ADAURA reported in the current submission reflect a data cut-off (DCO) of 11th April 2022 for DFS and 27th January 2023 for overall survival (OS).

(a) Why are the latest DCOs available for OS and DFS different?

(b) The most recent DCO for DFS is approximately 20 months ago, whilst the latest DCO is 12 months ago. Why are more recent data on DFS not available?

(c) Are any further data cuts of ADAURA anticipated (for DFS, OS or both)?

Response:

(a) & (b)
The planned analysis of DFS and OS were event-driven and not linked.

The planned DCO for the DFS (primary) event-based analysis was originally estimated to be February 2022. The ADAURA study protocol specified patients would not be followed for disease recurrence after the primary analysis but follow-up for overall survival would continue. After the IDMC met in April 2020 and reviewed the data, the committee recommended that the trial be unblinded at a trial level early and the April 2020 DCO became the primary analysis for DFS. As such, the DCO April 11, 2022 became final DFS analysis and was exploratory in nature. At the 11 April 2022 DCO, the DFS data was at the protocol specified maturity of approximately 50%.

The final OS was planned once the trial had reached 94 events, approximately 20% maturity, which was reached for the January 2023 DCO (18% maturity).

This information regarding planned DCOs for DFS and OS and expected data maturity were communicated by the Company during the original appraisal (TA761).

(c) [redacted]

B3. PRIORITY. CS, Section B.2.6.1.1, pages 46-47. The text states “Interpretation of the adjuvant osimertinib DFS curve beyond 48 months is limited due to censoring and low number of patients at risk, but is also expected to reach a plateau indicating patients are at low risk of recurrence.” At 48 months, 139 patients in the osimertinib group are still at risk (41% of the randomised osimertinib group), with the N at risk only becoming low after around 60 months. Please provide further justification for assuming a plateau in the osimertinib group of the economic model as well as further

justification for the timepoint at which this plateau is expected to occur in the osimertinib group.

Response:

Whilst the number at risk in the adjuvant osimertinib arm are still moderate at 48 months, the numbers at risk at timepoints beyond 48 months are much lower. It is well-established that surgical resection for early-stage NSCLC patients has curative potential, which is demonstrated by a plateauing in disease recurrence rates in post-surgical patients.[3] Clinicians also confirmed that in their clinical practice this patient group are discharged from care if they have not experienced disease recurrence within 5 years of receiving surgical resection. A plateau in disease recurrence can be observed in the placebo arm of the ADAURA trial at approximately 48 months, hence a plateau was also assumed for the osimertinib arm, but at a later time point (8 years), beyond the observed trial period. The assumption of cure at 5 years for the placebo arm was accepted by the NICE committee during the TA761 appraisal.

Interviewed clinicians have stated that they expect the significant DFS benefit observed with osimertinib in the ADAURA trial to translate to a greater proportion of osimertinib-treated patients achieving cure (seen as a plateau in the DFS KM-curve), compared with placebo (active monitoring).[6] The timepoint for assuming a cure assumption was discussed with clinicians and the 8 year timepoint was selected as a conservative assumption to allow for the established 5 years plus an additional 3 years of treatment with adjuvant osimertinib. Clinical experts in the 2020 survey were divided between a 5 and 8 year cure time point for osimertinib, and the 2023-interviews had a similar outcome; 3 out of 5 clinicians agreed that the 36 month treatment period for osimertinib should be accounted for whereas 2 out of 5 clinicians preferred that the cure time point should be 5 years in both arms, as there is no rationale why cure on the osimertinib arm would be later than in the active monitoring arm.[6,7] The 8 year cure assumption for the osimertinib arm also aligns with the ERG scenario termed as ‘pessimistic’ from TA761.[8]

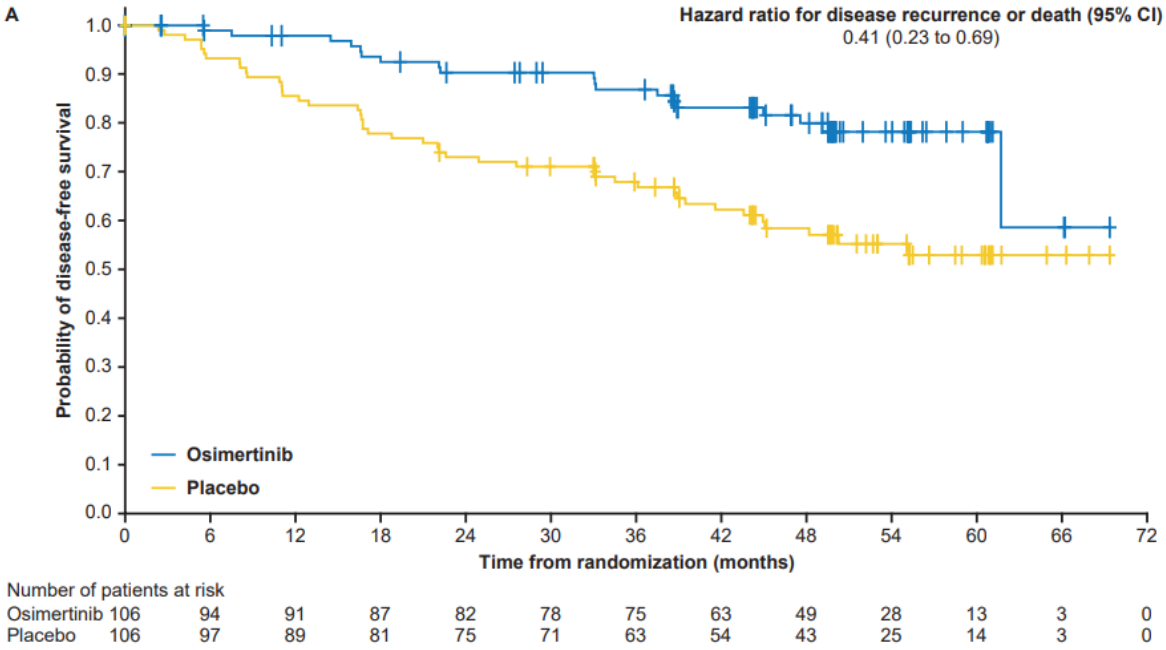
B4. CS, Section B.2.6, pages 46-58. The clinical section of the CS presents results for the overall ADAURA trial population and for the subgroup with stage II-IIIa

NSCLC. Please provide Kaplan-Meier plots of DFS, central nervous system (CNS) DFS and OS for the Stage 1B subgroup.

Response:

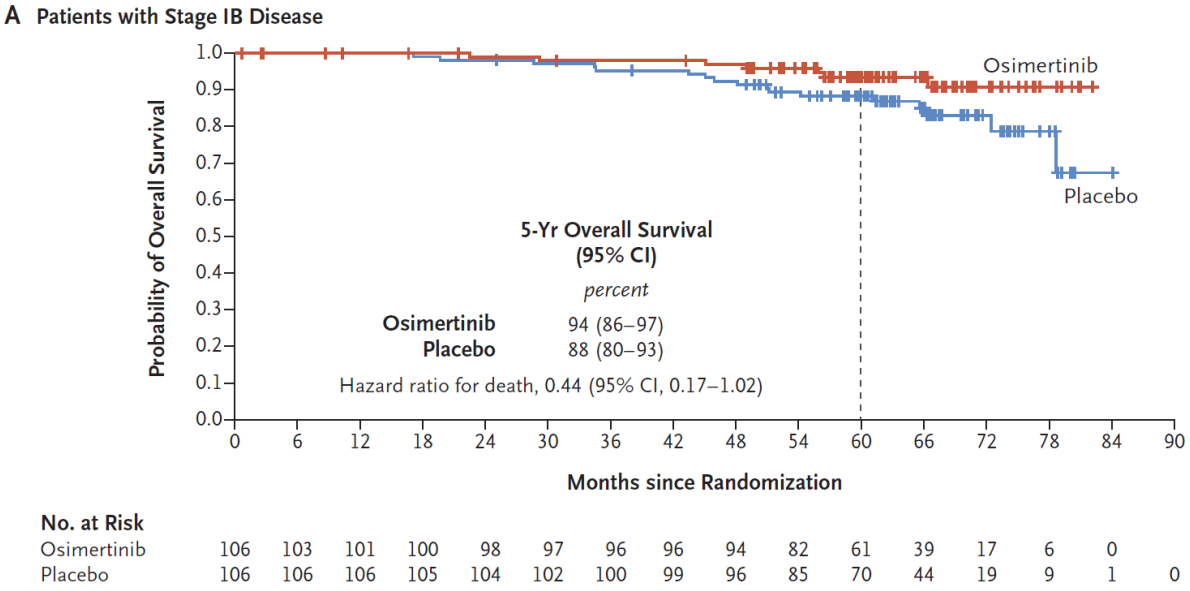
The Kaplan-Meier (KM) plots for DFS and OS for the stage IB subgroup are presented below which, while not powered for statistical significance, demonstrate a treatment benefit consistent with that observed in the overall trial population. A KM plot for CNS DFS is not available for the stage IB subgroup.

Figure 1. Disease free survival among Patients with Stage IB



Source: Herbst et al. 2023,[4] supplementary material 2

Figure 2. Overall survival among Patients with Stage IB



Source: Tsuboi et al. 2023[5]

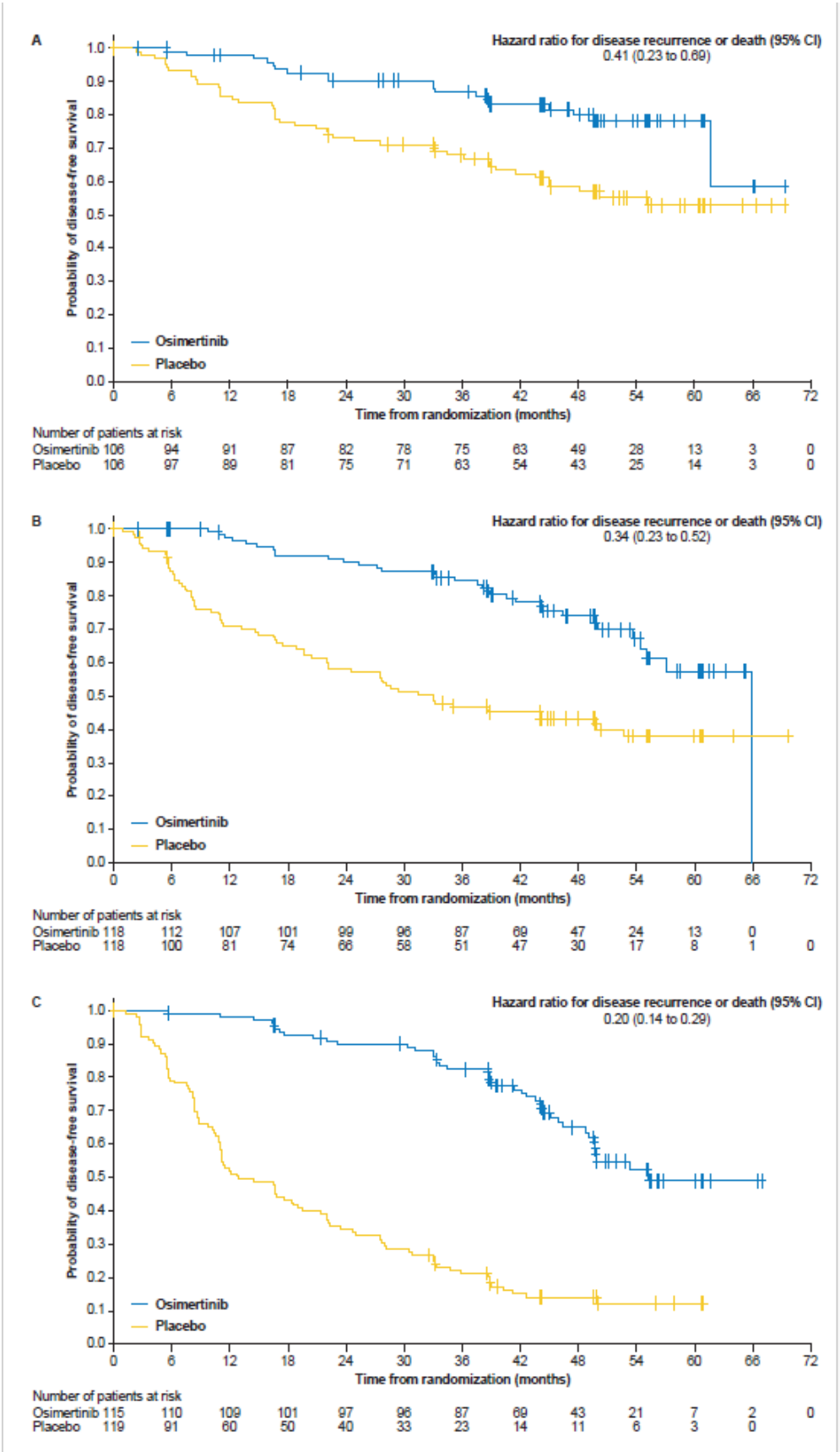
B5. CS, Section B.2.3.3, Table 9, page 42. Please clarify whether the data on stage at diagnosis presented in Table 9 of the CS relate to the 7th or the 8th edition of the American Joint Committee on Cancer (AJCC) classification.

Response:

Table 9 in the CS is the patient baseline characteristics at the time of enrolment. Staging is according to 7th edition AJCC classification. Table 11 in the CS demonstrates the differences in patient numbers by stage when patients were re-staged according to the 8th edition classification, which were largely consistent for each disease stage.

DFS plots by stage (IB/II/IIIA) by 7th vs. 8th edition staging are provided below to demonstrate the consistency in treatment effect, regardless of staging edition used.

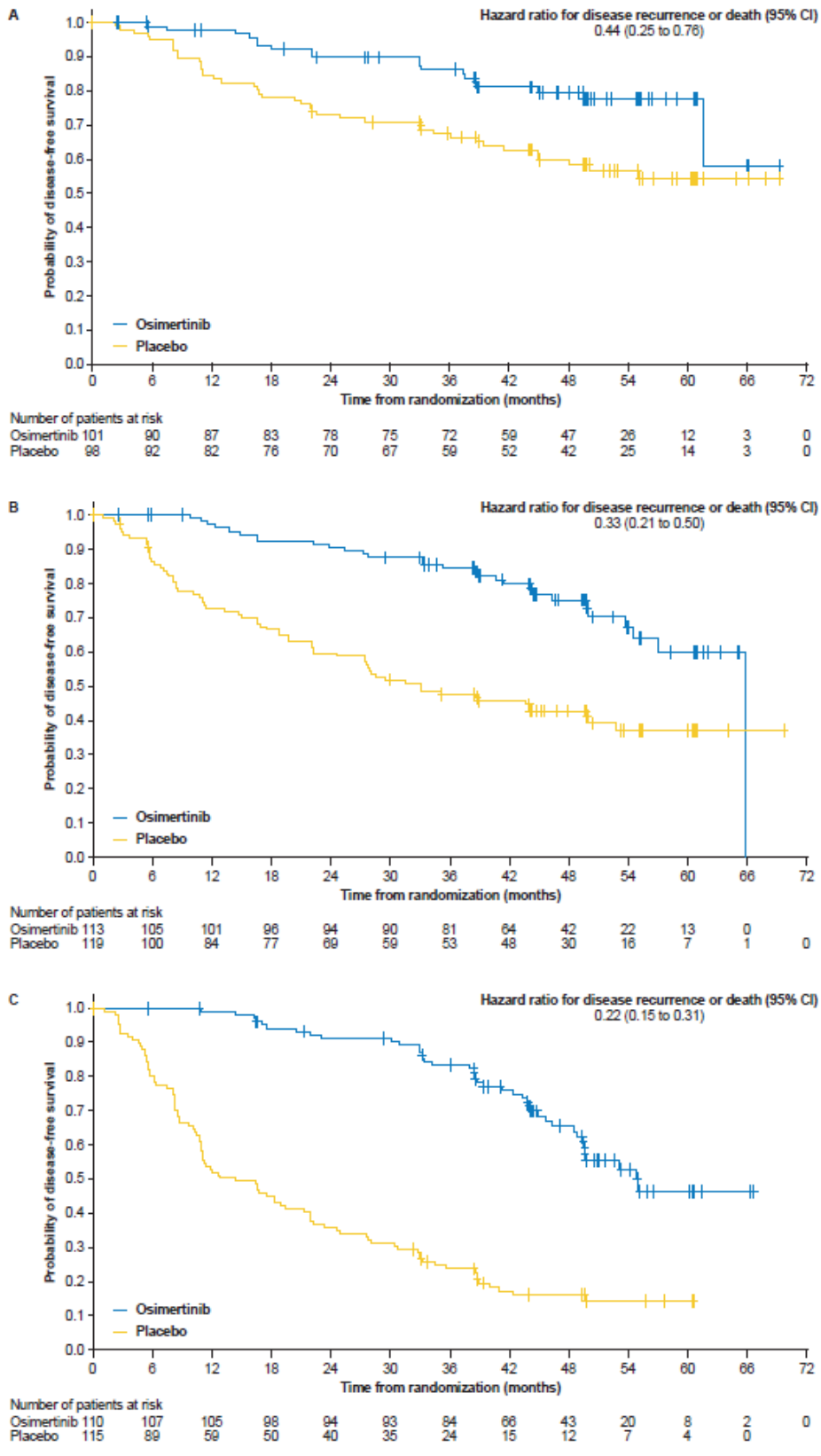
Figure 3. Updated disease-free survival by stage (AJCC/ UICC 7th edition)



A Stage IB, B Stage II, C Stage IIIA

Source: Tsuboi et al. 2023[5]

Figure 4. Updated disease-free survival by stage (AJCC/ UICC 8th edition)



A Stage IB, B Stage II, C Stage IIIA

Source: Tsuboi et al. 2023[5]

B6. CS, Section 2.6.1.1 Figure 8, page 50, Section 2.6.1.2 Figure 13, page 57 and Section B.2.3.3, Table 9, page 42. Figures 8 and 13 report on the same number of patients for the ADAURA subgroups with Stage IB/II/ IIIA disease (N=212/236/234, respectively). In Table 9, the total number of patients in each subgroup is different (N=216/231/235, respectively). Please explain these differences.

Response:

In the disease characteristics at baseline table, disease stage is as collected in electronic case report forms (eCRFs). However, when patients were stratified based on disease stage, interactive voice response system (IVRS) was used, hence the efficacy data, including the forest plots presented in figure 8 and 13, are based on staging as per the interactive voice response system (IVRS).

B7. CS, Section B.2.10.1, page 59. Please clarify the difference between “actual median exposure” and “total median exposure.”

Response:

Total exposure time was calculated from the first dose to the last dose. Actual exposure time was calculated from first dose to the last dose taking dose interruptions into account.

B8. CS, Section B.2.10.1.1, page 60. Tables 16 and 17 present data on adverse events (AEs) in ADAURA. The text on page 60 states “No new safety concerns were reported in the DCO of April 2022 or the final analysis (DCO January 2023) of ADAURA”. Please clarify which DCO was used for the AE data presented in the CS.

Response:

The AE data presented in tables 16 and 17 of the CS are from the Apr-22 DCO, at which point all patients had completed or discontinued the trial regimen. The safety analyses included adverse events with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy.

The safety data in tables 16 and 17 are consistent with the safety data reported in the Herbst et al. publication, which reports on updated analyses of final DFS, recurrence patterns and long-term safety. However, upon reviewing the table the Company has identified 2 errors: (1) n patients with any AE in the osimertinib arm should be 330, not 303; (2) the % of patients with a dose reduction in the osimertinib arm is 12 and not 13.

B9. CS, Section B.2.13.2.2, page 66. The text states "…compared with UK clinical practice where osimertinib is the first line treatment for over 80% of patients." Please clarify if this estimate of >80% from the IPSOS data relates specifically to patients receiving osimertinib for the first-line treatment for newly diagnosed metastatic disease, or whether it also includes patients receiving first-line treatment for metastatic relapse.

Response:

This estimate is for all first-line patients regardless of prior treatment. It should be noted that due to the timing of the adjuvant osimertinib CDF funding decision (Nov-21, i.e., less than three years ago) and the Blueteq criteria, which stipulates patients who have experienced disease progression while taking adjuvant osimertinib should not be retreated with osimertinib in the metastatic setting, it is not expected that the IPSOS data would provide insights on osimertinib re-treatment.

B10. CS, Section B.2.6.1.1, page 50, Figure 8 presents subgroup analysis of DFS in ADAURA. Please provide the DFS hazard ratios (HRs) and 95% confidence intervals (CIs) for with/without adjuvant chemotherapy within each stage. In other words, please provide the HRs of osimertinib versus placebo for Stage IB with adjuvant chemotherapy, Stage IB without adjuvant chemotherapy, Stage II with adjuvant chemotherapy, Stage II without adjuvant chemotherapy, and Stage IIIA with adjuvant chemotherapy, Stage IIIA without adjuvant chemotherapy separately. Please also provide equivalent subgroup analyses for OS.

Response:

Subgroup analyses by prior chemotherapy have only been assessed in the overall population (stage IB-IIIA) and not in the primary population (stage II-IIIA) or in individual stages (IB, II, IIIA). Additionally, the ADAURA trial did not power

subgroups for statistical significance and therefore subgroup analyses are exploratory in nature. Given there are between 107-126 patients in each arm of the trial when split by stage IB/II/IIIA, further reducing patient numbers to analyse outcomes by stage and prior chemotherapy use is not statistically robust and would not be informative for decision making, especially given the overall maturity of DFS is 45%.

Section C: Clarification on cost-effectiveness

Please note, when we reference the impact of a change on the ICER we are referring to changes relative to the original company submitted model. Some minor errors have been corrected in the Company model as suggested in the 'Executable model' section and the incremental impact of these have been demonstrated in Table 1 at the end of this document.

Review of previous models

C1. CS, Section B.3.1, pages 70-72. Please clarify if and how the published economic models of osimertinib were used to inform the approach taken and the assumptions made in the current economic model.

Response:

Four published cost-effectiveness models in adults with resected stage IB-IIIA NSCLC whose tumours harbour an EGFR mutation were identified. None of these models used a UK perspective.

The Verhoek et al. 2023[9] study employed a model consistent with the previously submitted model (TA761[8]); a 5 health-state semi-Markov model with a lifetime time horizon containing mutually exclusive health states for disease-free (DF), loco-regional recurrence (LRR), first-line distant metastatic disease (DM1), second-line distant metastatic disease (DM2) and death. The other three models identified (Lemmon et al. 2022,[10] Zhou et al. 2022,[11] Li et al. 2021[12]) were also all Markov models but of simpler structure, with health states limited to disease-free, progressed disease and death states. The 5-state approach adopted by Verhoek et al. 2023[9] was considered the most appropriate. Adjuvant osimertinib has demonstrated important efficacy benefits in reducing the proportion of patients who recur with

distant metastatic disease and instead recur in the locoregional-recurrence setting, and it was considered important to capture this in the model to increase accuracy in modelling health outcomes and costs. It was also considered important to model the DM1 and DM2 states separately due to the differences in treatment costs and outcomes and consideration for potential osimertinib re-treatment in the DM1 setting for those that received adjuvant osimertinib. The 5 health-state structure enables the capture of these alternative treatment costs and health outcomes.

Verhoek et al. 2023 was the only study to consider a lifetime time horizon. This was also considered the most appropriate approach for this setting given the potential for cure in this patient population, as it allows for costs and outcomes to be fully captured.

Model structure

C2. CS, Section B.3.2, page 72. The EAG understands that the economic model submitted to NICE to inform the current appraisal is based on the same general structure as the model used to inform TA761. Given that: (a) there are no relevant data for treatment duration or survival in a relapsed metastatic population (FLAURA was undertaken in newly diagnosed patients), and (b) calibration was required to force the model predictions of OS to better fit the observed OS data from ADAURA, please comment on the following:

(a) Whether a partitioned survival modelling approach was considered for the current appraisal and why this approach was rejected in favour of a semi-Markov model.

(b) The additional value of this semi-Markov model compared with a simpler partitioned survival model.

Response

a) and b)

A PSM was considered at model conceptualisation stage, but was rejected for the following reasons:

- **Uncertainty in OS extrapolations:** The extrapolations fit to the OS and DFS data in a PSM typically drive the model results. At the time of

the final analysis, 124 patients had died in the ADAURA population (18% maturity), of which 42 were in the osimertinib arm and 82 were in the active monitoring arm. Given this, there would be a lot of uncertainty in the OS extrapolations.

- **Capturing the long-term outcomes in the LRR, DM1 and DM2 health states:** In early-stage NSCLC, subsequent treatments are expected to have a considerable impact on long-term outcomes given the likelihood of different recurrence events (conditional on locoregional or distant metastasis) and multiple lines of therapy. Furthermore, since the treatment pathways are different between the osimertinib and active monitoring arm, this could not be reflected in a PSM. Therefore, a 'simpler PSM' would not capture the benefits of avoiding the LRR, DM1 and DM2 states.

Furthermore, as outlined in the response to question C1, all identified published models in osimertinib were either Markov or semi-Markov, rather than a simplified PSM. This approach to model structure is also consistent with previous NICE technology appraisals in early-stage cancer, including the original appraisal for adjuvant osimertinib (TA761, TA107, TA424, TA569, TA632, TA671, TA876 and TA823), and the model structure was discussed and validated at an independent UK clinical advisory board in November 2020.[13]

Survival modelling and calibration

C3. PRIORITY. CS, Section B.3.3.2, pages 81 to 124. The CS contains smoothed empirical and modelled hazard plots for transition probability (TP) 1 and TP2, but not for TP4, TP6, TP7 or TP8. Please provide these missing hazard plots. Please also explain whether and how consideration of the hazard functions was used to inform parametric survival model selection for transitions TP4, TP6, TP7 and TP8.

Response

Hazard plots were only used to aid with the selection of the transition probabilities that were informed by the updated ADAURA data (i.e., TP1 and TP2). These were the only transition probabilities that contained new data compared to the evidence submitted in TA761 (excluding the update to the general population mortality data).

Where data were not updated (TP4, TP6-TP8), extrapolations fit to these data were previously accepted by the committee in TA761, and there was limited discussion on the uncertainty surrounding the extrapolations selected.

Furthermore, the ICER is most sensitive to changes in the distributions selected for TP1 and TP2. The choice of distributions for TP4, TP6-TP8 has less of an impact on the ICER due to the maturity of the underlying data sources. The observed smoothed hazards compared to the modelled hazards have been provided below.

TP4 uses the CancerLinQ data to model the progression from LRR to DM1. In the base case, the lognormal curve was selected as it was the second-best fitting according to AIC/BIC statistics, and provided the best visual fit to the KM curve. A comparison of the smoothed observed hazard with modelled hazards confirms that the lognormal curve appears to be a reasonable fit for TP4, as it captures the initially higher hazard, which then decreases over time (see Figure 5).

Figure 5 Comparison of the smoothed observed hazard from CancerLinQ with modelled hazards for TP4

TP6 uses FLAURA data on time to discontinuation of treatment (TTD) to model the progression from DM1 to DM2. As outlined in Document B Section B.3.3.6.1, models fit independently to the osimertinib and active monitoring arms were considered appropriate. In the base case, the Weibull distribution was selected for both arms because it provided a good within-trial fit. For osimertinib it had the best AIC score and second-best BIC score; for active monitoring, it had the best AIC and BIC score. The visual fit of the KM curves to the Weibull curve also confirmed a good fit to the trial data. A comparison of the smoothed observed hazard with modelled hazards confirms that Weibull is a reasonable fit for the active monitoring arm, as it captures the trend towards increasing hazards overtime (Figure 6). For osimertinib, the hazard plot (Figure 7) suggests that a model with decreasing hazards over time may reflect the trial data better. For example, loglogistic may be considered a better option to capture this change in hazards, but upon visual assessment of the KM curves compared to the modelled curves (Figure 36 in ID5120_Osimertinib_Document B_[CIC]_10Jan24), loglogistic was considered to provide a worse fit compared to the Weibull distribution.

Figure 6 Comparison of the smoothed observed hazard from FLAURA (active monitoring arm) with modelled hazards for TP6

Figure 7 Comparison of the smoothed observed hazard from FLAURA (osimertinib arm) with modelled hazards for TP6

TP7 uses a combination of FLAURA data and UK life tables to model the progression from DM1 to death. When FLAURA is used, the data is pooled between arms for the time to death (censoring discontinuation of treatment) because of the low number of death events observed across treatment arms (n=11). None of the extrapolations were considered clinically plausible as they generally provide higher survival estimates than the application of background mortality rates. The exponential distribution was considered to have the most clinically plausible downward trend for patients in a metastatic setting and best statistical fit based on AIC and BIC values. This selection is confirmed by a comparison of the smoothed observed hazard with modelled hazards (Figure 8).

This distribution was applied until the hazard of the background mortality exceeds it. Thereafter, background mortality based on the age-adjusted UK population was applied.

Figure 8 Comparison of the smoothed observed hazard from FLAURA (pooled arms) with modelled hazards for TP7

TP8 uses a combination of FLAURA and IMPower150 to model the progression from DM2 to death. FLAURA data is used for the majority of patients. As outlined in Document B Section B.3.3.6.3, models fit independently to the osimertinib and active

monitoring arms from FLAURA were considered appropriate. In the base case, the Weibull distribution was selected for both arms because it provided a good within-trial fit, evidenced by having the lowest scored AIC/BIC for both arms. A comparison of the smoothed observed hazard with modelled hazards confirms that Weibull is a reasonable fit. An assessment of the observed hazards compared to the modelled hazards (

Figure 9 and Figure 10) shows that Weibull remains to be a good option to model this transition for both arms. While it may not pick up the sharp increase in hazards for the osimertinib arm of FLAURA, this is driven by a small number of patients at risk at the end of the FLAURA curve. Furthermore, when a distribution with increasing hazards is selected (i.e., generalised gamma), there is a minimal change in the ICER (£18,918.23).

Figure 9 Comparison of the smoothed observed hazard from FLAURA (active monitoring) with modelled hazards for TP8

Figure 10 Comparison of the smoothed observed hazard from FLAURA (osimertinib) with modelled hazards for TP8

C4. PRIORITY. CS, Section B.3.3.2, pages 81 to 124. Please provide plots of the time-varying HRs for DFS and OS for osimertinib versus placebo in ADAURA, based on the latest DCOs for each endpoint.

Response:

The DFS hazard ratio (HR: 0.27; 95% CI: 0.21, 0.34) for the overall population at the final DFS analysis (Apr-22 DCO) was consistent with the DFS hazard ratio (HR: 0.20; 99.12% CI: 0.14, 0.30; p<0.001) at the time of the primary analysis (Jan-20 DCO). As outlined in the CS (pg. 46), interpretation of the adjuvant osimertinib DFS curve beyond 48 months is limited due to high levels of censoring (67.8% at final DFS analysis) leading to low number of patients at risk. The placebo arm had similarly low numbers of patients a risk at later timepoints driven by the higher disease recurrence or death rates (70.5%). As such, the latter period of a piecewise hazard ratio analysis for DFS would be highly uncertain, and given the censoring in the osimertinib arm, overly conservative. In terms of OS, due to the relative immaturity at the Jan-23 DCO (18% maturity), the ADAURA OS data are not used in the model, which is consistent with the original appraisal (TA761). The calculation of

time-varying HRs was not a pre-specified analysis in the SAP and for the reasons outlined above are not considered appropriate as a post-hoc analysis for the DFS or OS data from ADAURA.

The violation of the proportional hazards assumption for transition probabilities derived from the DFS data has been acknowledged elsewhere in the CS (section B3.3) and appropriate steps have been taken to ensure there is sufficient flexibility in modelling methodology to accurately capture the DFS hazards e.g., by fitting independent models, selecting the best fitting parametric models per treatment arm for each TP, and applying varying cure assumptions per arm. Overall, this results in a modelled aggregated DFS curve (CS, figure 44) which is a good visual fit to the ADUARA DFS KM and meets clinical expectations. It provides an arguably conservative estimate of treatment effect given it underestimates the adjuvant osimertinib curve and overestimates the placebo arm in the within trial period. Overall, due to the consistency in DFS between the two DCOs, the good visual fit of the modelled DFS curve, and the validation from clinical experts, plots of time varying HRs would not have a material impact on the DFS analysis or model outcomes.

C5. CS, Section B.3.3.3.2, page 89 and 96. The text indicates that some parametric survival models for TP1 and TP2 were excluded on the basis that they are not aligned with expectations of cure. However, given that the model includes a separate structural assumption of cure, which overrides the parametric survival model predictions, please explain why any consideration of cure was necessary when selecting preferred parametric survival models for inclusion in the economic model.

Response:

The model implements a structural cure, hence why the curves for TP1 and TP2 were only considered to 5 and 8 years for active monitoring and osimertinib respectively. The process followed for selecting the most appropriate survival extrapolation for these transitions consisted of assessing the goodness of fit statistics (AIC and BIC), hazard plots, visual fit of the KM curves to the extrapolated curves, and asking clinical opinion where possible. Although 95% of the patients are considered to be cured after 5 or 8 years, for active monitoring and osimertinib respectively, that leaves 5% of the patients in every model cycle who are assumed

not to be cured and still have a chance of recurring. Clinical experts agreed that also for these patients the risk should be decreasing or plateauing over time. Therefore,

parametric models that had a plateau were considered to be a better clinical fit.

For osimertinib TP1, this meant that the Weibull, loglogistic, and Gompertz modelled hazards were predicting increasing hazards overtime and considered to be overly influenced by the tail of the curve which has higher censoring and lower number of people at risk.

For osimertinib TP2, it was recognised that whilst the exponential hazards did not capture the changes in the hazards sufficiently, the Weibull and Gompertz models were predicting sharply increasing hazards overtime and considered to be overly influenced by the tail of the curve which has higher censoring and lower number of people at risk.

None of the active monitoring curves for TP1 and TP2 were ruled out in this manner, and model selection was primarily based on statistical fit and visual fit (both of the observed hazards and KM curve to the model predictions)

Given that the clinicians validated the DFS curves which were based on models with plateauing hazards, the final combination of curves selected were considered clinically viable.

C6. PRIORITY. CS, Section B.3.3.3.1, pages 82 to 88. The NICE Guidance document for TA761 states that “more formal statistical modelling of cure may address some uncertainty.” This has not been done in the current CS as mixture-cure models (MCMs) have been fitted only to data from the control arm of the ANITA trial. Please fit MCMs to the aggregate data on DFS and OS for each treatment group in ADAURA. We do not need you to attempt to incorporate these MCMs into the economic model. Please present the following outputs for each endpoint:

(a) Plots of observed versus MCM-predicted survival

(b) Estimated cure fractions

(c) Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics.

Response:

The ANITA study had a median follow-up of 76 months in the chemotherapy group and 77 months in the observation group and the disease-free survival KM curves extend beyond 100 months (>8 years). In comparison, the median follow-up for DFS in the ADAURA trial was 44.2 months for the adjuvant osimertinib patients and 27.7 months in the active monitoring patients with DFS KM curves extending to 72 months, but with limited numbers of patients at risk from 60 months (5 years). Given the established timepoint for cure in post-resection early-stage NSCLC patients not treated with adjuvant osimertinib is 5 years, and is estimated to be 8 years for the adjuvant osimertinib patients, the DFS data from the ADAURA trial is not sufficiently mature enough to robustly fit MCMs. Use of MCM modelling for the ADAURA data is also limited due to the trial size. That MCMs are usually less fit to be applied directly to an RCT is also recognized in NICE DSU TSD 21 ("In small datasets there may be issues around the practicality and plausibility of being able to reliably estimate the cure fraction"). The fitting of an MCM to ADAURA data would result in unreliable cure estimates due to the immaturity of the data in the context of the expected cure timepoints, particularly for the adjuvant osimertinib arm, where the KM curves have not yet reached a plateau. As well as being the most appropriate method based on the availability of data from the ADAURA trial, the structural cure assumption applied in the model has been clinically validated and is supported by the MCM analysis outlined in section B.3.3.3.1 of the CS.

C7. PRIORITY. CS, Section 3.3, pages 79 to 124. Please confirm that all Kaplan-Meier plots for individual components of the composite endpoints presented in this section of the CS (Figures 20, 26, 32, 34, 38, and 40) include censoring for the event not of interest (e.g., in Figure 20, is DFS censored for deaths and distant recurrence?).

Response:

We confirm all Kaplan-Meier plots for individual components of the composite endpoints include censoring for events not of interest.

C8. CS, Section B.3.3.6.1 to B.3.3.6.3, pages 108 to 119. Please clarify if the underlying OS data from FLAURA have been updated since TA761. If not, please clarify why not.

Response:

The FLAURA data used in TA761 was the TTD and OS data from the 25 June 2019 DCO. This was the final FLAURA DCO hence, this data has not been changed or updated since TA761.

C9. PRIORITY. Executable model, worksheet "Transitions", columns FB and LW. The parameters of the log-logistic, log-normal, Gompertz and generalised gamma survival models for TP8 contained in this worksheet are the same for both the osimertinib and TKI groups. This appears to be an error. Please correct this in a revised version of the economic model.

Response:

This has been revised in the model as detailed in Table 1. There is no impact on the base case ICER.

C10. PRIORITY. CS, Section 3.3, pages 79 to 124. The visual fit of some of the parametric survival models, particularly for TP1 and TP2, is weak. Please clarify why restricted cubic spline (RCS) models were not included in the survival analysis described in the CS. Please fit RCS models to the data for TP1 and TP2, including models with up to 3 knots, fitted on the hazard, odds and normal scales. Please also update the economic model to include functionality to select any of these parametric survival models for TP1 and TP2 in each treatment group.

Response:

The standard models were not considered to be a poor visual fit to the KM curves for TP1 or TP2, particularly given the timeframe these extrapolations are used (5 and 8 years). The fit of the observed smoothed hazards to the modelled hazards is also considered to be good for the majority of the time period, however, does fit less well at the end for the osimertinib arm due to a combination of a low number of events and low number at risk at the tail (see Document B Section B.3.3.3.2 and B.3.3.3.3). Therefore, splines were not considered appropriate given that standard models

provided a sufficiently good fit to the data, and given the immaturity of the data and because of the low number at risk at later time points.

Given the PH assumption is violated, parametric models were independently fit to each arm in the ADAURA trial and the best fitting distribution was selected (as outlined in Document B, Section B.3.3.3.2 and B.3.3.3.3). Additionally, a structural cure assumption with a warm-up period was applied at 5 and 8 years in the active monitoring and osimertinib arms, and the resulting curves with the cure assumption applied then aligned with clinical expectations in this setting. This also validates the long-term extrapolation selection for TP1 and TP2. The curve selection in combination with the cure assumption is considered suitably flexible to appropriately capture the trial hazards plus a range of plausible scenarios.

In summary, the Company has taken a parsimonious approach to fitting the modelled curves and this has resulted in overall aggregated DFS curves fitting well to the ADAURA KM curves and, as outlined in the response to Q C4, represents an arguably conservative estimate of outcomes. As such, fitting RCS models to the data in TP1 and TP2 is unlikely to further improve the fit of the data and would not have a material impact on decision-making.

C11. PRIORITY. CS, Section B.3.3.4, page 102. The economic model includes an adjustment ("calibration") of the survival models used to estimate TP4 (locoregional recurrence [LRR] to distant metastasis [DM] 1), TP6 (DM1 to DM2) and TP8 (DM2 to dead). This calibration is done by adjusting the survival model (or sometimes part of the survival model) using a single HR of [redacted] for each transition. Please address the following questions regarding this calibration approach:

(a) Please clarify why calibration was deemed necessary in the current appraisal, but not in TA761.

(b) Please justify why the same value of [redacted] is applied to each calibrated transition probability.

(c) Please clarify whether the executable model includes the Solver procedure used to perform the calibration process, and if not, please provide an updated version of the economic model which allows the model to be recalibrated.

(d) The text states “A scenario was conducted where the calibration factor is not applied, see section B.3.8.3.” However, this analysis is not presented in Section B.3.8.3. Please provide this analysis and comment on the results.

(e) The text in Section B.2.13.2.2 states “Less than half of patients in the placebo arm of ADAURA received osimertinib as their first subsequent therapy for metastatic disease compared with UK clinical practice where osimertinib is the first line treatment for over 80% of patients.” The model applies the costs of osimertinib in DM1 to 83% of patients in the active monitoring group. However, the DFS and OS functions used in the calibration reflect a population in which less than 50% of patients received osimertinib for metastatic relapse (as described in the quote above). Was the model calibrated against an active monitoring group in which less than 50% of patients receive osimertinib in DM1, or one in which 83% of patients receive osimertinib in DM1?

(f) Below, we have summarised how the calibration factor is applied to the transition probabilities estimated from each of the fitted parametric survival models. Please explain why the calibration factor is only applied to part of the survival model in TP6, and why it is not applied at all in TP7.

- **Adjuvant osimertinib group**
    - TP4. Applied to all patients.
    - TP6. Applied to those re-treated with osimertinib in DM1, but not to those receiving chemotherapy in DM1.
    - TP7. Not applied.
    - TP8. Applied to patients receiving chemotherapy, but not those receiving ABCP.
- **Active monitoring group**
    - TP4. Applied to all patients.
    - TP6. Applied to all patients.
    - TP7. Not applied.
    - TP8. Applied to patients receiving chemotherapy, but not those receiving ABCP.

Response:

a) The ADAURA OS data was <5% mature at the time of TA761 and therefore assessment of fit of the modelled curves to the KM data was limited. Whilst limited by maturity, the aggregated modelled OS curves aligned with the ADAURA OS KM curves and adjustment was not required. Since increasing in maturity, the difference in aggregated modelled OS curves, compared with the ADAURA OS KM has become more apparent due to the differences in baseline patient characteristics in the FLAURA vs. ADAURA populations (i.e., resected vs. not resected). Hence, an adjustment to account to account for differences in patient populations is now required.

b) As outlined in the CS (section B.3.3.4), as the model predicts DFS well but not OS, TP1 and TP2 were not calibrated. TP3, TP5 and TP7 were not calibrated as it would be inappropriate to reduce the risk of death below that of the general population. The overall calibration factor was calculated by determining the difference between the ADAURA OS KM and the aggregated modelled OS, as the ADAURA data was not sufficiently mature to enable calibration of each individual TP. As TP4, TP6 and TP8 are all considered to be limited by the same rationale equally across both arms in the model i.e., all required calibrating due to differences in patient populations versus the ADAURA trial, the calibration factor was also applied equally for each TP across both arms. The difference between the observed and predicted OS was assessed by calculating the mean squared error (MSE). There are endless combinations possible to minimize the MSE when using different CFs for each TP. Using the same CF for each TP reduced the MSE to close to zero, so there was no mathematical need for further divergence. This approach was discussed with health economic and clinical experts, who preferred having one CF instead of a separate CF per TP.

c) When calculating the appropriate calibration factor for these TPs, a version of the cost-effectiveness model was set to replicate the ADAURA trial as closely as possible to generate the most reliable calibration factor. This included replicating the subsequent therapies as per ADAURA trial. The Excel solver function was then used to calculate the calibration factor. Since the subsequent therapy replication requires different treatment percentages in

LRR and DM1, this was a separate model. As such, the Excel solver function cannot be made available in the current model.

d) This scenario has been added, where the calibration factor is set to 1 (i.e., no adjustment to the TPs). This has a minimal impact on the ICER, which increases from £18,967 to £22,356.

e) As outlined in the response to part (c), the calibration factor adjusts for differences in patient baseline characteristics. In order to calculate the adjustment as accurately as possible a version of the model was set up to replicate the ADAURA trial as closely as possible, which included matching the subsequent treatments to those received in the trial as closely as possible. The calibration factor was then applied to the model when subsequent therapies were set to distributions more reflective of UK clinical practice. Adjusting subsequent treatment distributions impacts both costs and efficacy. Hence, applying the subsequent treatment adjustment and the calibration factor via this method provides a more robust estimate of cost-effectiveness in a UK setting when both subsequent treatments and baseline population characteristics are adjusted for.

f) The efficacy for chemotherapy in TP6 and ABCP in TP8 were derived via different sources unrelated to ADAURA and FLAURA (a NMA HR was applied for chemotherapy and the IMPower150 trial was used to inform the ABCP efficacy as described in Document B Section B.3.3.6). Therefore, it was deemed inappropriate to apply a CF derived on ADAURA and FLAURA data on these external data. Additionally, if a CF was applied to the PDC patients in DM1 of the osimertinib arm, this would improve efficacy in the adjuvant osimertinib arm and thereby reduce the ICER. Applying the CF to the 20% of patients in both arms who receive ABCP is unlikely to have a significant impact on the ICER due to the relatively small proportion of patients who receive this line of therapy.

C12. PRIORITY. CS, Section 3.3.3.1, page 87. The executable model applies a "warm-up" period for the cure timepoint in each treatment group (from 48 to 60 months in the active monitoring group and from 48 to 96 months in the adjuvant osimertinib group). This is an unconventional approach to modelling cure – most

economic models of potentially curative therapies submitted to NICE either apply a structural assumption of a cure timepoint or use MCMs to estimate a cure fraction. Please clarify:

(a) Why this approach to cure was adopted.

(b) Whether the warm-up approach was suggested by the company, or by the clinical experts.

(c) Whether the company is aware of any prior NICE appraisals which have also applied a warm-up period for a structural cure assumption.

(d) Whether the company or the clinical experts determined the starting and final timepoints for the warm-up periods in each treatment group.

Response:

a) The Company does not consider this approach as unconventional. This was the same approach that was presented and accepted in TA761. The application of a warm-up period was considered more clinically plausible by clinical experts compared to assuming an immediate application of the cure assumption from a one-time point. In interviews with clinical experts in November 2023, some commented that they would expect the cure timepoint to be the same in both arms (i.e., 5 years). Adding the treatment period to the osimertinib arm to assume cure from 8 years without warm-up was considered too pessimistic, as it does not capture the proportion of patients who would otherwise be cured at 5 years without adjuvant osimertinib. The inclusion of a warm-up period is therefore considered a conservative middle ground. Furthermore, a plateau in the DFS curves in the active monitoring arm can be observed from approximately 48 months, hence applying a warm-up period from this time point and reaching 95% cure at 60 months is considered a reasonable approach and produces a more clinically plausible DFS curve compared with applying cure at 5 years without a warm-up period. For the osimertinib arm, while a plateau is not observed in the within-trial period, it is reasonable to assume that the proportion of patients who would achieve cure without adjuvant osimertinib are also present in this curve and therefore would demonstrate the same survival dynamics as the active monitoring arm. Therefore, the warm-up period in the osimertinib arm was

started at the same timepoint as the active monitoring arm to appropriately capture these patients who would achieve cure at 48-60 months regardless of having received adjuvant osimertinib treatment, but the cure rate was increased over 48 months rather than 12 to allow the curve to capture the decrease in DFS rate due to patients who may experience disease recurrence after 60 months. As with the active monitoring arm, applying the warm-up period results in a more clinically plausible DFS curve, which is a good visual fit to the ADAURA DFS KM. Clinical experts were presented this approach in the November 2023 interviews (see Figure 9 in 'AZ data on file. ADAURA NICE CDF exit submission. KEE report.pdf'). Clinicians agreed that a gradually increasing percentage of patients could be assumed to be functionally cured before the five-year treatment-free mark is reached. Clinicians agreed with the both the starting timepoint (48 months in both arms), the warm-up period (12 months in the standard of care arm and 48 months in the osimertinib arm), and the final cure percentage (95%).

b) This was the same approach that was presented and accepted in TA761. A similar approach was also used and accepted in TA632 (early-stage breast cancer).

c) and d) The Company based the starting and final time points on the committee-accepted values used in TA761. The clinicians validated these values.

Subgroup analyses

C13. Please provide a subgroup analysis to assess the cost-effectiveness of adjuvant osimertinib versus active monitoring for patients with Stage 1B disease.

Response:

Despite the perceived inherent reduction in the risk of recurrence or death in patients with earlier stages of NSCLC, there remains a significant unmet need to improve outcomes for these patients. Whilst complete surgical resection is performed with curative intent, there remains a significant risk of relapse and disease progression in patients with stage IB disease with studies showing that 45% of patients with stage

IB NSCLC recur within 5 years following surgery.[4,5] In addition, a pooled analysis from 5 large NSCLC trials which included data from 4,584 patients demonstrated that just 62% patients with fully resected stage IB NSCLC survive for 5 years, and this is similar to data reported by Cancer Research UK, which reveals that just 62.7% of patients diagnosed with stage I NSCLC will survive for at least 5 years.[5,14] As such, there is a significant need to improve the outcomes for patients with stage IB NSCLC.

The ADAURA clinical study demonstrated a consistent DFS benefit across all subgroups, including by stage of disease with 95% CI overlapping with the overall population. In addition, despite the early nature of the disease, adjuvant treatment with osimertinib resulted in a significant 59% reduction in the risk of disease recurrence or death for the stage IB subgroup (HR: 0.41; 95% CI: 0.23, 0.69) compared with placebo, further supporting the significance of the benefit across all patients enrolled in the study. However, due to the reduced risk of recurrence in patients with stage IB disease vs those with more advanced disease, the data in patients with stage IB disease are highly immature, with just 19 and 44 events reported in patients receiving osimertinib vs placebo, respectively, at the time of the latest data cut-off. Furthermore, the study was not powered to assess the efficacy in patients by stage of disease. Therefore, due to these significant limitations it would be inappropriate to assess the cost-effectiveness of osimertinib in patients with stage IB disease alone as the data are not suitable to inform decision-making.

Re-treatment with osimertinib

C14. PRIORITY. CS, Section 2.6.2, page 58. The text states that data on the level of re-treatment with osimertinib, which formed a key uncertainty in TA761, were not collected through SACT. Please clarify why these data have not been collected and whether any other data source, besides clinical opinion, could provide estimates of osimertinib re-treatment rates.

Response:

At the original appraisal of osimertinib (TA761), the NICE committee concluded that SACT data collection was unlikely to provide meaningful data on the proportion of patients that would be retreated with osimertinib in clinical practice in a reasonable

timeframe, but considered this acceptable as this assumption made no significant difference to the cost effectiveness estimates. Therefore, NHS England only collected data on treatment duration and overall survival. Other uncertainties, including the proportion of patients retreated with osimertinib, were expected to be included in the ADAURA clinical trial results.

Subsequent treatment data from the ADAURA trial was provided in Appendix Q of the Company submission. The trial found [redacted] of patients in the in the adjuvant osimertinib arm who received a first post-study anti-cancer therapy received osimertinib as re-treatment. This data was not used to inform the model because it is immature, and it is unknown whether a patients progressed on or after adjuvant osimertinib. Furthermore, due to different country reimbursement policies for the countries involved in the ADUARA trial it is not feasible to use the ADAURA trial directly to inform retreatment practice in the UK.

Real-world evidence studies are expected in the future to address retreatment rates, but the Company is not aware of any further data sources that are available at present.

C15. PRIORITY. Page 108, Section B.3.3.6, page 107. The text states “the economic model assumes that 50% of patients would be retreated at the five–year time point, and alternative proportions are also explored in scenario analyses.”

(a) Please clarify the source of this assumption.

(b) Please provide details of any estimates of osimertinib re-treatment rates provided by the clinical experts during the 2023 interviews.

(c) Please clarify how many patients were re-treated with osimertinib in ADAURA.

Response:

(a) Clinical experts indicated that patients did not progress whilst on adjuvant osimertinib, or had completed three-years of treatment and then progressed, they would consider retreatment. This assumption is consistent with the accepted re-treatment assumption in TA761.

(b) No clinicians had enough experience with the need to consider retreatment in practice.

(c) Subsequent treatment data from the ADAURA trial was provided in Appendix Q of the Company submission and demonstrates [redacted] of patients in the ADAURA trial who received a first post study anti-cancer therapy received osimertinib. However, due to different country reimbursement policies for the countries involved in the ADUARA trial it is not feasible to use the ADAURA trial directly to inform retreatment practice in the UK.

Adverse events

C16. Model, worksheet "Adverse events", cells G32:G37 and I32:I37. Please clarify the source of the AE frequencies used in the model. The EAG notes that these values do not appear to match the values reported in the ADAURA clinical study report (CSR) or CSR Addendum 1.

Response:

Grade 3 or higher, causally related to treatment AEs that occurred in at least two patients in either treatment arm in the ADAURA trial were included in the model. These AE are reported in Table 14.3.2.5 of the CSR (DCO: Aril 2022) and match those used in the model.

Executable model

Please note, all updates to the base case ICER described in the section below detail the impact when the model amendment is made in isolation to the originally submitted model. Table 1 provides details of all changes in code, the impact on the original ICER and new base case ICER. An updated model with all changes as been provided separately ('ID5120_Osimertinib_Cost Effectiveness Model_Updated_[CIC]_12Jan24.xlsm').

C17. Model, worksheets "TP Matrix Osi" and "TP Matrix Placebo", column X. The proportion of patients cured does not rise in equal increments in each cycle; rather, the increase in the cured proportion in last cycle before reaching 95% cure is higher than the increase between other previous cycles. Please clarify if this is an error and correct it in a revised version of the model.

Response:

This has now been revised in the model by extending the cure for one more cycle, ensuring the cure proportion rises in equal increments in each cycle as detailed in Table 1This amendment had a negligible impact on the base case ICER, which decreased from £18,967 to £18,732.

C18. Model, worksheet "Transitions", vertical text labels in columns A, W, AS, BO, CK, DG, EC, EY, FV, GR, HN, IJ, JF, KB, KX and LT. In this worksheet:

(a) Please amend these headings so that they clearly describe the treatment arm within the trial, rather than the treatment group in the economic model. For example, is the vertical text in column DG labelled as "osimertinib arm" describing the treatment group of the model, or the treatment group in the FLAURA trial? Is the vertical text in column KB labelled "placebo" intended to reflect the TKI arm of the trial?

(b) Please add clear labelling in this worksheet to indicate which transition probability and which sub-model in the trace each survival model is used to inform.

(c) Please clarify which Kaplan-Meier estimates in worksheet "Kaplan-Meier curves" each block of survival model parameters corresponds to.

Response:

a and b) The vertical text labels in the Transition sheet have been updated to reflect which arm from which trial is being modelled.

c) The headers in the Kaplan-Meier curves worksheet have been updated to match the labels as discussed in point a).

C19. Model, worksheet "TP Matrix Osi", cells VC12:VC60 and cells APF61:APF532. The model includes separate DM1 sub-models for patients who receive adjuvant osimertinib and then are re-treated and for those who are not re-treated. Page 108 of the CS states that 50% of patients are assumed to be re-treated after 4 years. However, the model assumes that after 4 years, all patients who enter DM1 go to the re-treatment sub-model. Please explain why this approach has been used. Why does the model not instead assume that 50% of patients who transition to DM1 after

48 months go to the re-treatment sub-model, and 50% go to the no re-treatment sub-model?

Response:

The sub-models are split up into the period before and after retreatment is possible. The first sub-model contains all patients who enter DM1 within 4 years since randomization (not modelled to receive retreatment with osimertinib), whereas the second sub-model contains all patients who enter DM1 4 years after randomization (able to receive retreatment with osimertinib). The second sub-model then applies a weighted efficacy for DM2 treatment based on the percentage retreated with osimertinib and the percentage who receive chemotherapy in DM1. This approach was followed to be able to differentiate patients who receive chemotherapy in DM1 and are then treated with docetaxel in DM2, and patients who progress after 4 years, receive chemotherapy after 48 months, and are treated with pemetrexed+cisplatin.

C20. PRIORITY. Model, worksheet "Trace Placebo", columns AS, AT and AU. The calculations in these columns include the costs of drug acquisition, administration, and disease management in DM2 for patients (where 83% received osimertinib and 17% received an early TKI in DM1).

- Treatment administration and acquisition costs are missing for: (a) the costs of PDC in the 80% of people who received osimertinib in DM1, and (b) the costs of ABCP in 20% of the people who received an early TKI in DM1.
- Disease management costs are missing for: the whole group of people who received an early TKI in DM1.

Please confirm that these are errors and provide a corrected version of the model.

Response:

This has now been revised in the model as outlined in Table 1. This amendment had a minor impact on the base case ICER, which decreased from £18,967 to £17,034.

C21. Model, worksheet "Trace Placebo", column AP. These calculations include a one-off CNS metastases cost (named cell reference "cost_cns_one_off"). However, this cost is only applied to those patients who receive osimertinib in DM1 – the costs for patients who receive an early TKI in DM1 have been erroneously excluded

(column APJ in worksheet “TP Matrix Placebo”). Please confirm this is an error and provide a corrected version of the model.

Response:

This has now been revised in the model as detailed in Table 1 by expanding the calculation to include the patients receiving early TKI in DM1. This amendment had a negligible impact on the base case ICER, which decreased from £18,967 to £18,427.

C22. Model, worksheet “Parameters”, cells E199, E200, E201 and E202. These calculations erroneously exclude the frequency and cost/disutility of decreased ejection fraction. Please confirm that these are errors and provide a corrected version of the model.

Response:

This has now been revised in the model as detailed in Table 1 by including the frequency and cost/disutility of decreased ejection fraction. This amendment had a negligible impact on the base case ICER, which increased from £18,967 to £18,986.

C23. Model, worksheets “TP Matrix Placebo” and “TP Matrix Osi”, column H. The formulae in this cell range assume that the proportionate split of men and women remains constant at every age, yet the life table probabilities indicate that men and women have different age-specific risks of death. Both of these cannot simultaneously be true. Please amend the model to use a weighted survival model, based on separate survival models for men and women, with the weighting applied at baseline.

Response:

Assuming a constant proportion of women/men at every age was a pragmatic and simplified approach. It was not considered necessary to use a weighted survival model and was anticipated to result in minor changes to the results.

However, the model has been amended with a weighted survival, where the weighting is applied at baseline (where lx and dx are reweighted using the male/female distribution and qx is calculated accordingly). This change was performed as a scenario analysis only, rather than base case amendment, and did not have an impact on the base case ICER, which remained at £18,967.

C24. Model, worksheet “Trace Osi”, column R. The check calculations in this cell range do not sum to 1.0 at all timepoints. Please investigate this error. Note that the active monitoring trace is not subject to this error.

Response:

The Company acknowledges that that there was a discrepancy in the model, where the first cycle of deaths in DM1 was not taken into account. This resulted in a rounding error, where the check calculations were off by 1e-9. This has now been revised in the model as outlined in Table 1. This amendment did not have an impact on the base case ICER, which remained at £18,967.

C25. Model, worksheets, “Trace Placebo” and “Trace Osi”, column AU. These calculations apply the disease management costs in DM2 including the CNS metastasis costs. Please explain why one-off CNS metastasis costs are not included in DM2. Are you assuming that all CNS metastases occur whilst on first-line therapy?

Response:

In the ADAURA trial, 51 patients in the osimertinib arm experienced distant metastatic disease recurrence compared to 127 patients in the placebo arm. From these, 22 patients experienced CNS disease recurrence in the osimertinib arm (equating to 43.1%) and 39 patients experienced CNS disease recurrence in the placebo arm (equating to 30.7%).

Additional resources for patients in the distant metastases health states were applied to the proportion of patients with CNS metastases to capture the additional burden of this complication. This was applied first as one-off cost to account for the initial diagnosis and receival of stereotactic or whole brain radiotherapy in DM1 using the percentage above. After that, incremental costs are applied in both DM1 and DM2 to account for the ongoing management of CNS metastasis. Hence, CNS metastases are indeed assumed to occur in DM1 as there is no data available to differentiate by health state, and costs for treatment is applied in both DM1 and DM2. However, the cost of ongoing management of CNS metastases was not applied in DM2 to the group of patients receiving early TKI in DM1. That has been addressed and slightly

decreased the ICER from £18,967 to £18,323, see also the response to C21. Detail on how this was addressed in the model is outlined in Table 1.

C26. Model, worksheet, "Survival", cell H32:K32,H33:K33. The range included in these formulae should start from row 12 and continue until row 456 (from cycle 0 to 444) rather than from row 1 to row 532. Please confirm that these are errors and provide a corrected version of the model. Please note that these values are not half-cycle corrected.

Response:

This has now been revised in the model as detailed in Table 1.This table is purely illustrative and this change does not impact the base case ICER.

C27. Model, worksheets, "Trace Osi" and "Trace Placebo", column AF. The calculations apply the disease management costs in the DFS state. After 48 months, the DFS management costs become zero. Given the assumption that 95% of patients are cured after 8 years for osimertinib and after 5 years for active monitoring, please explain why DFS management costs are not incurred between months 48 to 96 months in the osimertinib arm or between 48 to 60 months in the active monitoring arm.

Response:

Acknowledging that uncured patients in DFS should receive disease management costs until the final cure time point. This has now been revised in the model as detailed in Table 1 by assigning DFS management costs to the uncured patients until 8 years for osimertinib and 5 years for active monitoring. This amendment had a minor impact on the base case ICER, which increased from £18,967 to £21,556. Detail on how this was addressed in the model is outlined in Table 1.

C28. Model, worksheet, "Trace Osi", column AS and AT. The calculations in these columns apply the treatment administration and acquisition costs in DM2 for both the non-retreated and retreated groups. The administration costs and acquisition costs of second-line docetaxel in DM2 are missing for 50% of the re-treated group (those

who received PDC in DM1). Please confirm that these are errors and provide a corrected version of the model.

Response:

Both the administration and acquisition costs for the second-line docetaxel in DM2 of the 50% retreated group are accounted for via the below part of the formula: "(1-(prop_IMPower_followingTKI*(1-dm1_retreatment_perc_chemo)))" which serves as a catch-all for all patients who do not receive the ABCP-regimen in DM2 and therefore receive chemotherapy instead.

C29. Model, worksheets, "Trace Osi" and "Trace Placebo". Column AI. The calculations apply the treatment administration costs in LRR. The last two lines of the formulae relate to the next cycle rather than the current cycle. Please explain why these formulae are not consistent with the other cost calculations in these two worksheets.

Response:

This has now been revised in the model as detailed in Table 1. This amendment had no impact on the base case ICER.

HRQoL

C30. CS, Section B.3.4.1, pages 124 to 129. Please clarify which DCO in ADAURA has been used to estimate EQ-5D from the trial. Has this analysis been updated since TA761? If not, please explain why not.

Response:

Data from the Jan-20 DCO were used to estimate EQ-5D from the trial. This analysis was not updated at the time of the Apri-22 DCO as sufficient HRQoL data was available to estimate EQ-5D and derive appropriate utility values from the previous DCO. Additionally, the SF-36 scores appeared consistent between DCOs (see CSR table 27 and CSR addendum 1 table 11) and an updated mapping exercise would be unlikely to materially impact the utility value for the DF state, which is applied. The same utility values were applied in TA761 and additional sensitivity analyses were conducted using utility values from the Andreas et al. 2018 study,[15] which had a limited impact on the cost-effectiveness estimates. The ERG also noted the utility

values used in the base case in TA761 did not necessarily favour osimertinib, which also applies to this appraisal. Overall, the committee for TA761 concluded the Company's utility values were acceptable for decision-making.[8]

C31. CS, Section B.3.4.6, page 133. Utility values are adjusted using Ara and Brazier (2010). Please provide an updated version of the model which uses age-adjusted utility values from Hernandez Alava *et al.* (https://www.sheffield.ac.uk/nice-dsu/methods-development/estimating-eq-5d)

Response:

This has been amended in the model, where the age-adjusted utility values from Hernandez Alava et al. are applied as an age-adjusted multiplier using the age of 63 as starting year and the 30%/70% distribution of male/female. This was conducted as a scenario analysis only and had a negligible impact on the base case ICER, which decreased from £18,967 to £18,403.

C32. CS, Section B.3.4.6, Table 40, page 133. The estimated utility value in the DF state from ADAURA is higher than that for the general population (based on Hernandez Alava *et al.*). Please constrain the DF utility value by general population utility in an updated version of the model.

Response:

The use of the DF utility value per ADAURA trial was discussed and accepted in the previous appraisal (TA761), where the ERG conducted additional sensitivity analysis using utility values from Andreas et al. (2018) and concluded that this had a limited effect on the cost-effectiveness estimate. The committee concluded that the DF utility value per ADAURA trial were acceptable for decision making. Nevertheless, a scenario analysis has been conducted where the DF utility is based upon Hernandez Alava et al., which estimates the general population utility for an age of 63 and 30% male at 0.8210. This scenario showed that the impact is indeed minor; the ICER increased by 0.99%.

C33. CS, Section B.3.4.2.2, Page 125-126. A repeated measures mixed effect (RMME) model is used for the utility analysis. Please clarify whether baseline

utility values and end of trial observations are included in the response variable and justify the reasons for including or excluding these.

Response:

Before conducting the RMME analysis, descriptive statistics were run including the utility over all observations. As utility over all observations was constant, there was no reason to consider end of trial observations as covariates. Instead, three covariates were considered in the RMME analysis; the baseline utility values, adverse events and treatment effect. Each was first tested as univariate analysis, which showed that baseline and adverse events (AE) were statistically significant (p-value <0.001 and 0.048, respectively), but treatment effect was not (p-value of 0.408). Therefore, only baseline and AE were considered in the multivariate analysis (including interaction terms) where backwards selection was applied until only statistically significant covariates remained. This resulted in the final model with baseline and AE as covariates.

C34. CS Section B.3.4.2.3, Figure 46 and Table 32, page 127. The figure and table suggest that the mean utility for osimertinib is lower than placebo at multiple time points. This finding is also reflected in Table 33, where the mean utility for osimertinib without Common Terminology Criteria for Adverse Events (CTCAE) Grade 3+ AEs is lower than that for placebo without CTCAE Grade 3+ AEs. Please explain the reasons for this. Please also comment on why the mean utility for osimertinib with CTCAE Grade 3+ is higher than that for placebo with CTCAE Grade 3+, as suggested in Table 33.

Response:

As described in the response on C33, treatment effect was tested as covariate, however, no statistical differences were found between osimertinib and placebo. This was also the case when testing the interaction effect between CTCAE Grade 3+ AEs and treatment.

C35. CS Section B.3.4.2.3, Page 127. Please clarify the reference group used in RMME univariate analyses of covariate 3 (treatment effect) presented in Table 34.

Response:

The placebo-arm was the reference group used in RMME univariate analyses of covariate 3.

Costs

C36. CS, Section B.3.5.2.1, Table 41, page 137. The model assumes that people who are treated with adjuvant osimertinib and are not re-treated in DM1 go on to receive PDC in DM1 and docetaxel in DM2. Why do none of these patients receive ABCP in DM2? Please amend the model, if necessary.

Response:

The ABCP regimen is recommended for use post-progression while receiving an EGFR-TKI for advanced EGFRm NSCLC. Is it not positioned for use within the pathway after progression while taking PDC in the NG122 lung cancer guideline.[16] This is in line with the IMpower150 trial, which demonstrates the efficacy of ABPC for first-line treatment of advanced NSCLC in patients who had not previously received chemotherapy and only included patients with EGFR or ALK genomic mutations if they had experienced disease progression with or unacceptable side effects from treatment with at least one EGFR-TKI in the advanced setting.[17] The submitted model is in line with the clinical pathway and the evidence for the use of ABCP in this patient population, therefore, the model has not been amended.

C37. PRIORITY. CS, Section B.3.5.2.1, Figure 47, page 136. Please clarify which DCO in ADAURA has been used to estimate time to treatment discontinuation from the trial. Has this analysis been updated since TA761? If not, please explain why not.

Response:

TTD data from the final DFS analysis (DCO: Apr-22) has been used. This is a more recent data cut than the one used for TA761. At the Apr-22 DCO, all patients had had the opportunity to receive 3 years of adjuvant osimertinib treatment and, therefore, further follow-up for TTD was not conducted as there was sufficient follow-up data to directly observe time on adjuvant treatment without the need for additional extrapolation.

C38. PRIORITY. CS, Section B.3.5.2, page 135. The model does not include any costs associated with EGFR testing. Please include this cost in model, based on the

number of patients needed to test to identify one patient with an EGFR mutation (with exon 19 deletions or exon 21 (L858R) substitution mutations).

Response:

Multi-target NGS panel testing, which includes EGFR, is included in the NHS national genomic test directory and is part of routine care for all early-stage NSCLC patients. As such, the testing cost is common to both arms of the trial and has not been included.[18]

C39. CS. Section B.3.5.2.5, page 142. The text states "It was assumed that patients treated with osimertinib in the DF state require less monitoring than patients treated with osimertinib in the DM state." The frequency of resource use per cycle for monitoring for osimertinib in the DM1 state is twice that of monitoring for osimertinib in the DFS state. Please justify why the resource use for treatment-related monitoring should be different between the two states, clarify the source of this assumption, and explain whether clinical experts agreed with it.

Response:

The frequency of monitoring in the DF and DM states is consistent with those used in TA761, and was supported by consultations with clinical experts.[7]

Discounting

C40. CS, Section B.3.8.3, Table 62, page 173. This table includes a scenario labelled as "QALY discount of 1.5% to cured patients." This scenario applies the 1.5% discount rate only to the proportion of cured patients in each cycle (including the warm-up period). This is an unconventional approach. Please justify why discounting has been applied differentially between the cured and uncured patients in the economic model.

Response:

Section 4.5.2 of the NICE manual states "alternative analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis, in specific circumstances".[19] The criteria for applying the 1.5% discount rate are: (1) the technology is for people who would otherwise die or have a very severely

impaired life; (2) it is likely to restore them to full or near-full health; (3) the benefits are likely to be sustained over a very long period. Given adjuvant osimertinib fulfils this criteria, it is appropriate to apply the 1.5% discount rate in a scenario analysis. Given not all patients will be restored to full health, the Company has taken the conservative approach of applying the 1.5% discount rate to only the cured proportion rather than the full modelled population.

Summary of all changes to model

A summary of all the technical changes made to the model are provided in Table 1 . This excludes changes made as part of a scenario (i.e., changes in response to C23 and C31).

Table 1 Overview of all changes made to the model

Q	Location	Old formula	New formula	New ICER	% change vs. base case ICER
CS base case ICER (filename: 'ID5120_Osimertinib_Cost Effectiveness Model_Final [CIC]_10Jan24.xlsm') : £18,967.24					
C9	Transitions!LX36-MO52	Contained osimertinib coefficients instead of placebo coefficient	Replaced coefficients with correct values for placebo	£18,967.24	0.00%
C17	TP Matrix Osi!X and TP Matrix Placebo!X	[redacted]	[redacted]	£18,732.05	-1.24%
C20	Trace Placebo!AS:AU	[redacted]	[redacted]	£17,034.49	-10.19%

		[redacted]	[redacted]		

		[redacted]	[redacted]		

		[redacted]	[redacted]		

		[redacted]	[redacted]		

		[redacted]			

		[redacted]			
C21	Trace Placebo!AP	[redacted]	[redacted]	£18,426.58	-2.85%
C22	Parameters!E199-E202	[redacted]	[redacted]	£18,985.58	0.10%
C24	TP Matrix Osi!VD	[redacted]	[redacted]	£18,967.24	0.00%
C25	Trace Osi!AU	[redacted]	[redacted]	£18,322.87	-3.40%
C26	Survival	[redacted]	[redacted]	£18,967.24	0.00%
C27	Trace Osi!AF and Trace Placebo!AF	[redacted]	[redacted]	£21,556.31	13.65%
C29	Trace Osi!AI and Trace Placebo!AI	[redacted]	[redacted]	£18,967.38	0.00%

		[redacted]	[redacted]		
All changes applied: new Company base case (ID5120_Osimertinib_Cost Effectiveness Model_Updated_[CIC]_12Jan24)				£16,446	-13.29%

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Follow-on questions 16/02/24

We have scrutinised the company's post-clarification model and we believe that there remain some errors in this updated model version. Please can the company confirm that these are errors, and if possible, fix the errors.

Issue 1. Following on from clarification question C20, first bullet, point (b). In the active monitoring group, the costs of treatment acquisition of second-line ABCP following first-line early TKI appear to be incorrect for 2 reasons:

- In worksheet "Trace Placebo", column AT, the part of the calculation which relates to atezolizumab in ABCP only refers to cell P12, not the array of values in column P.
- In the same set of calculations in column AT, the calculations refer to an array in the sub-model which misses out the first cycle ('TP Matrix Placebo'!BJN11:CDM11 instead of 'TP Matrix Placebo'!BJM11:CDM11).

Response:

The formula in the worksheet "Trace Placebo", column AT, has been updated/simplified to account for the complete vector. This results in a minimal change to the ICER (decrease of 1.66%).

Issue 2. Following on from clarification question C21, the updated model includes a "change log" which explains the company's correction to CNS management costs. However, this correction has not been implemented in the updated model itself.

Response:

The correction has been implemented now to "Trace Placebo", column AP. This results in a minimal change to the ICER (decrease of 3.25%).

Issue 3. Following on from question C28, worksheet "Trace Osi", column AT. The acquisition and admin/monitoring costs of second-line docetaxel after PDC in the osimertinib re-treated sub-model are still missing from the calculations. This issue also applies to column AS.

You can see this issue is present by setting the duration of the waiting period before retreatment to zero (cell J36, "Settings" worksheet), then changing the cost of docetaxel (cell E301,"Parameters" worksheet) to a different number. The total disease management costs in DM2 does not change. This shows that the updated model is missing the costs of docetaxel in both columns AS and AT.

Response:

The acquisition and admin/monitoring costs of second-line docetaxel after PDC in DM1 are included in the calculations for the osimertinib no-retreatment sub-model and the re-treated sub-model. This can be validated through the steps outlined below.

Docetaxel in the no-retreatment sub-model:

Changing the cost of Docetaxel in the no-retreatment subgroup via the worksheet 'TX Patterns', cell L59 does change the acquisition cost in DM2. Changing the market share of Docetaxel via the worksheet 'TX Patterns', cell I59 changes both the administration cost and acquisition cost in DM2.

Docetaxel in the re-treated sub-model:

By default, the percentage of patients receiving second-line docetaxel after PDC in the osimertinib re-treated sub-model are set to 0%. Therefore, changing these costs have no impact on the results. Changing the percentage via the worksheet 'TX Patterns', cell J68, and then changing the costs of docetaxel via the worksheet 'TX Patterns', cell L68, show that the costs for second-line docetaxel after PDC in the osimertinib re-treated sub-model are included in the calculations.

Note that the disease management costs are not impacted by the cost of docetaxel, as this category is used for i.e. healthcare resource usage costs.

Issue 4. Following on from question C27, disease management costs. The updated model extends the duration over which these costs are applied, but only for uncured patients. The EAG does not believe that this approach makes sense, because it is not possible to determine which patients will or will not be cured (at least not prior to the assumed cure timepoint). The EAG believes that the correct approach would be to extend disease management costs for the osimertinib group to 8 years for all patients. Please confirm that you agree.

Response:

In consultation with UK clinicians the disease management in DFS was discussed (2020 and 2023 interviews). Clinicians stated that their usual practice is to cease follow-up of patients after 5 years. Therefore, the company believes that the current approach is correct and appropriately reflects the UK clinical pathway.

As the cure assumption for the osimertinib arm is gradually applied from 0% at 48 months up to 95% at 96 months, there remains some uncured patients after 5 years. However, patients are not tracked so it is not possible to determine which patients will or will not be cured before 96 months.

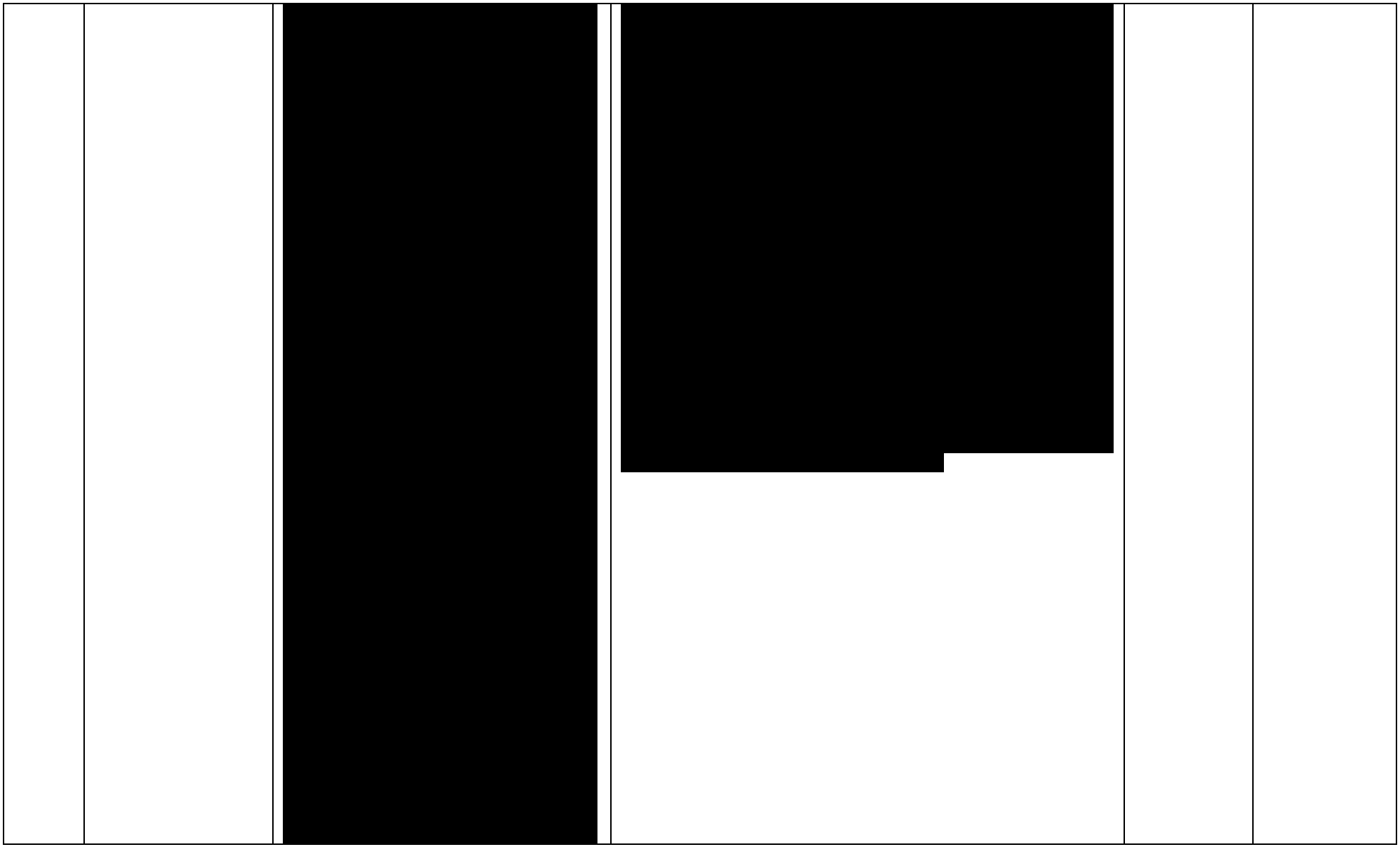
A scenario has been added to show that the extension of disease management cost for the osimertinib group to 8 years for all patients, and 5 years for the placebo group, has a minimal impact on the ICER, which increases from £15,656 to £17,518 (11.9%). However, the Company believe that this is a conservative approach, and in UK clinical practice the ICER would fall somewhere between these values.

Summary of the changes to model

A summary of the technical changes made to the model are provided in Table 1. This excludes changes made as part of a scenario (i.e., changes in response issue 4).

Table 1 Overview of the changes made to the model

Issue	Location	Old formula	New formula	New ICER	% change vs. base case ICER
CS base case ICER (filename: 'ID5120_Osimertinib_Cost Effectiveness Model_Updated_[CIC]_12Jan24.xlsm') : £16,445.91					
1	[redacted]	[redacted]	[redacted]	£16,173.05	-1.66%



		[redacted]			
2	[redacted]	[redacted]	[redacted]	£15,911.66	-3.25%
Changes applied: new Company base case (ID5120_Osimertinib_Cost Effectiveness Model_[CIC]_23Feb24.xlsm)				£15,656,25	-4.80%

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Guidance review following a period of managed access - Patient organisation submission

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

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 20 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	EGFR Positive UK
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	EGFR Positive 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 have 677 members.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of 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 Facebook group which is the main forum for the exchange of information. As we have 677 members we are able to present a representative view of the experience of living with EGFR mutation positive lung cancer. For this submission I have drawn on the experiences of 5 EGFR+ patients and my own personal experience. 3 of the patients, all of whom started treatment during the MAA period, were interviewed to capture their experience of taking Osimertinib following a complete resection.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to	Non-small cell lung cancer (NSCLC) with an EGFR mutation is an aggressive disease that has a considerable physical, psychological, economic and social impact on patients and their families. Patients affected by EGFR positive NSCLC are generally younger than typical lung cancer patients, non-smokers, more likely to be female, often still working and with a dependent children. The diagnosis therefore is particularly devastating, often coming as a total shock.

your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	Patient writes: 'I was diagnosed 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 is very hard to cope with'. A lung cancer diagnosis causes immense strain. Many of our patients and loved ones suffer from anxiety and depression as they wonder what the future will hold. This coupled with the burden of disease and treatment, impacts enormously on the quality of life of the patient and their families. Psychologically, socially and economically life can be extremely challenging. The family income can be impacted and normal family activities such as holidays and outings are interrupted or no longer possible. Recent members who have joined our group include a thirty seven year old father with 3 children under the age of 5 and a forty-three year old mother with a 10 and an 8 year old. Patient writes: 'I feel robbed of my future. All those memories I may never have a chance to make. My kids leaving school, going to university, getting married, starting a family…' Learning that surgery is a possible and potentially curative treatment is welcomed by the patient. There is significant positive psychological impact in knowing that the cancer will be removed. Once recovery from surgery in underway the greatest fear becomes one of recurrence and how this can be prevented. Patient commented: ‘following surgery I was offered 4 cycles of chemotherapy. I had recovered well from the surgery but the chemo was very tough and in the end I only had 3 cycles as I became so poorly. The recurrence figures for EGFR+ are frightening and I was told that the chemo would only give me 5% improvement. I now wonder whether it was worth it’. Another patient was offered Osimertinib following surgery Patient : ‘when you have surgery you think it is all fixed but it isn’t. The combination of Osimertinib and regular scans makes me more optimistic and that it is the best it can be. My quality of life is pretty good and Osimertinib has given me a lot of hope. But I am 69yrs old, it may be different for the younger ones’.

	Close monitoring can help alleviate some of the fear of recurrence but not all patients are offered the same monitoring schedule: Patient A: Stage 2b, Osimertinib and 3 monthly CT scans and bloods, brain MRI if becomes symptomatic Patient B: Stage 2a, Osimertinib and 6 monthly CT scans and bloods, annual brain MRI Patient C: Stage 1a, tumour 2.9mms, Osimertinib not offered. After 18 months of quarterly x-rays and an annual CT scan he is now moving to 'no further monitoring' with the directive to go to his GP if he experiences symptoms. He had previously been told that he would be monitored for 5yrs. He says 'I feel abandoned, having been told that if it is coming back it will be between 3-5 years. Weird to stop scanning when it is most likely to come back. Waiting 'til symptoms will be too late, surely better to catch it early. It is a strange kind of torture and I can't get my head around it!' This change from the original monitoring plan has affected his whole family. 'I am usually very laid back but just now I'm on edge. I get angry quickly and I feel guilty. I shouldn't be moaning about this, there are others worse off than me. My wife says I'm much quieter, more reserved but inside I am really angry – how dare they abandon me!. This is not fair, but there is nothing I can do about it.' Fear of recurrence of disease and knowing that the time on Osimertinib is currently 3 years, carries a high psychological burden on the patient and their family. Patient B: 'I worry about what will happen after 3 years when Osimertinib will stop. Do we all just sit back and wait for it (the cancer) to come back as we know it probably will and then re-start Osi? I am at the 18 month stage and have a good quality of life. Will I still get scanned? I am getting more anxious as I get closer to the 3 year point.' Only one NICE approved TKI (Osimertinib) offers protection to the brain and as brain metastases are common with this disease, patients who are not on this drug fear a recurrence of the disease in the brain. Crucially, our members testify that their quality of life is significantly improved on Osimertinib, both in terms of fewer, less harsh side effects, less time spent at hospital and GP appointments or receiving treatments for side effects.

	Additionally once brain metastases are identified the patient must stop driving, this has implications for both the patient and their families. Patient B comments: 'if I were to lost my driving licence my husband would need to go into care, there's no-one to help with all the things I do for him. He would be housebound. I can't imagine how we would cope.' Patients deserve the chance of treatments which will give them as much time as possible with their families and the ability to continue to actively their lives as long as possible.
7. What do carers experience when caring for someone with the condition?	Family and carers for patients may have a considerable burden providing care and assistance with the activities of daily living. This could affect the ability of family members to continue employment, have a detrimental effect on household income, and cause financial strain. This may add to the stress and anxiety of caring for a loved one with significant disease that may or may not return. For younger family members, educational choices may be affected which can have an impact for years to come. What happens if the patient is a carer? Patient B: 'The impact of it coming back is huge for us. I am a full time carer for my husband who had a stroke 15 years ago. I am doing remarkably well following my surgery and time on Osimertinib. Neither me nor my husband have made much call on the NHS other than my regular scans and medication. We rarely go to the GP. I am also economically active and help look after my grandchildren. If my cancer returns my husband will need full time residential care and the NHS will be paying for 2 of us, that should be part of the cost benefit analysis. Me being unable to care for him, will have a high actual and emotional cost to our whole family and the NHS.' Osimertinib is well tolerated. The once daily oral formulation is convenient for patients to take and does not disrupt day-to-day life with hospital appointments for administration. Family members welcome a treatment which allows the patient to have the best quality of life possible and over time they adjust to their loved ones illness and fear the future less. Sadly this is rarely the case for the patient.

	Patient A: 'I am doing well but sometimes I think that because I am doing well, everyone thinks it has gone. It hasn't. It is my head and at times I am caught by it, like when the kids are making plans for the future.' Families are greatly reassured when they see their loved one not only coping with their disease but able to do most of the things they did before. Regular monitoring and a drug that protects from recurrence is an additional psychological boost.
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	Resection alone does not 'cure' this disease and the high rate of recurrence calls for an additional step in the treatment path. Patient D: 'Following the resection my initial diagnosis was T2aN1(stage 11B) and at this point I was offered adjuvant chemotherapy with 'curative intent'. It was explained to me that this had to be completed quickly as possible as beyond a certain amount of time from the operation it's impact lessens. I was left with the distinct impression that the chemo was not altogether necessary and I would probably not have taken up the option of Chemo. Complete resection is emotionally powerful as it takes away the active cancer. Anything that then suggests a possible cure is to be grabbed but not if it is only partially effective'. Most patients dread Chemo. The logistics of the treatment, time cost and the side effects, all at a time when one is recovering from a major operation is tough. When compared to a highly efficacious daily tablet taken in your own home, chemo falls short. Chemo also does not offer any protection to the brain and therefore carries a significant risk of symptomatic central nervous system (CNS) metastases. Patient B: 'I don't take being here for granted but I have a chance and with Osimertinib a really good chance'.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition?	There is no agreed standard of care in relation to how a patient is monitored following resection. This will result in some patients being disadvantaged and risking recurrence possibly when the disease has progressed beyond the point of treatment.

If yes please state what these are	Patient C comments: 'it (not having adjuvant treatment) feels like a cross your fingers and hope strategy. Am I cured, will it come back? The sense of unfairness is enormous. There is something out there that could deal with this but I am not allowed it'. Resection followed by adjuvant Osimertinib is the standard of care in many countries. Knowing that there is another treatment that is more effective than the one you are on is very upsetting and exasperating. Patient D: 'my resection was in Vienna and there I was told my treatment would be surgery followed by a TKI so long as histology confirmed I had EGFR+ or ALK+. Upon return to the UK I was only offered chemotherapy.'

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	Patients have been able to access and have the treatment. An exception is patient C who was not offered adjuvant Osimertinib as his tumour was 2.99mms not 3mms which his Oncologist said was the required size.

11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Treatment with adjuvant Osimertinib allows patients to experience a good quality and live disease free for longer and possibly be cured. This would likely result in more independence with day-to-day life and selfcare, which would reduce dependence on family and support services. Many of the members of the EGFR+ patient community have been on more than one TKI and the general consensus is that Osimertinib has fewer and less extreme side effects than older generation TKIs or chemo..
12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Cost If Osimertinib is prescribed in the adjuvant setting 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.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	Patient B: 'I definitely think it (adjuvant Osimertinib) is worth it. It's a no-brainer, especially compared to Chemo and I have had both'.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	Hospital visits are difficult for anyone but especially those with mobility or cognitive issues. A daily tablet taken at home will ease this pressure for this group of patients. Taking a single daily tablet is easier for anyone to incorporate into their daily routine. Some patients are very anxious about recurrence. Having an additional treatment that gives greater protection against recurrence is very reassuring to these patients.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	Not known

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

The major inequality is related to equitable access to treatment. This is in part due to the differing healthcare regulations across the UK but also the differing level of knowledge and experience of Oncologists and their Clinical teams. What would be considered to be common practice in one area is seen as radical treatment in another.

Section 7 Other issues & Topic Specific Questions

21. Are there any other issues that you would like the committee to consider?

22. Would Osimertinib ever be use used in place of adjuvant chemotherapy (i.e. would people choose to have Osimertinib instead of chemotherapy)?

Most fellow patients with EGFR+ dread the move to Chemo. The logistics of the treatment, time cost and the side effects, all at a time when one is recovering from a major operation is tough. Comparing this to a highly efficacious daily tablet taken in your own home means that chemo is found wanting.

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement

- Resection 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 resection is recurrence.. 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.
- An agreed standard of care in relation to how a patient is monitored following resection and a drug that protects from recurrence are crucial for these patients who have a good chance of living well for many years.
- Continued use of Osimertinib after 3 years is not recommended. If after 3 years the patient continues to do well, removing Osimertinib is harsh, unless it can be evidenced that the patient will not be disadvantaged by this action.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Single Technology Appraisal

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

Clinical expert statement

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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.

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 **12 April 2024.** 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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Part 1: Treating EGFR mutation-positive non-small-cell lung cancer (NSCLC) after complete tumour resection and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Elizabeth Toy
2. Name of organisation	Somerset 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 NSCLC after complete tumour resection? ☐ A specialist in the clinical evidence base for EGFR mutation-positive NSCLC after complete tumour resection? ☐ 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 organisation's submission)	☐ 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.)
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 NSCLC after complete tumour resection? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To reduce the risk of recurrent cancer and eliminate micrometastases. and to extend both disease free and overall survival
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)	Given this is adjuvant treatment it isn't possible to assess response whilst on treatment. Imaging is performed to rule out recurrent disease. We know that even after curative surgery 5 year survival rates decrease from 90% to 24% (as stage increases) due to local recurrence and metastatic disease. An improvement in overall survival of 4-5 % which is seen in the use of adjuvant chemotherapy is recognised as being clinically significant in the treatment of NSCLC and appropriate to this cohort of patients. 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 NSCLC after complete tumour resection?	Yes outside the managed access scheme there are no treatment options after chemotherapy to prevent or delay disease recurrence. Recurrent disease has a devastating effect on both patients and their families.
11. How is EGFR mutation-positive NSCLC after complete tumour resection 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	Lung Cancer services in England are commissioned to be delivered using the Optimal Lung cancer Pathway and follow NICE Guidance (NG122) which recommends adjuvant chemotherapy but also reflects more recent advances made and availability of drugs through the Cancer Drugs Fund (CDF) Standard practice in England reflects current international guidelines from European Society of Medical Oncology (ESMO) and American Society of Clinical

across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Oncology (ASCO) with platinum doublet-based chemotherapy being recommended for patients with Stage II-IIIA disease and select patients with Stage1B disease. For patients whose tumour expresses a PDL1 level of >50% the immunotherapy drug Atezolizumab would also be added to the regimen and be continued for 12 months in total. (ASCO Guidance would be for PDL1>1%) The ESMO and ASCO Guidance also recommends Osimertinib after compete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours exhibit EGFR exon 19 deletions or exon 21 L858R substitution mutations. The Get it Right First Time (GIRFT) lung cancer programme and National Lung Cancer Audits demonstrate variation in surgical resection rates and access to adjuvant treatment between Lung cancer MDTs in the UK. Moreover, these rates are recognised to be lower than treatment rates in Europe, Recommendations were made in the National GIRFT report to increase the rate of adjuvant chemotherapy to ensure rates are > 40% The current patient pathway should follow: 1) All patients suitable for resection should be discussed in a multidisciplinary MDT with genomic and PDL1 results to consider whether neo-adjuvant chemo immunotherapy indicated. 2) Surgical resection 3) Post operative review of pathology and if the patient has not received neoadjuvant therapy the patient should be considered for referral to oncology to consider appropriate adjuvant therapy. Patients known to have an EGFR activating mutation would generally not be recommended for neo-adjuvant therapy as it is recognised that they have less benefit from immunotherapy agents. The adoption of this technology should reinforce the need for genomic testing to be brought forward in the patient pathway.

	Since it's availability through the CDF patients with cancers of an appropriate stage have been offered either single agent Osimertinib for 3 years or 4 cycles of platinum doublet chemotherapy followed by Osimertinib. I do not think that adoption of the technology will affect overall chemotherapy rates, however I believe it will increase the overall uptake of adjuvant treatment given the clear benefits and acceptable toxicity profile.
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 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?	Yes the updated results from the ADAURA trial show highly clinically significant improvements in overall survival, disease free survival and a reduction in intracranial disease. This represents a significant breakthrough in the patient care.

• Do you expect the technology to increase health-related quality of life more than current 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 survival and freedom from disease. There is a significant adverse impact on quality of life at the point of cancer recurrence following potentially curative surgery.
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.
15. 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)	Oncology services are very experienced in the management of patients receiving Osimertinib for stage IV NSCLC. 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.
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 ADAURA study. Treatment would continue for three years 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 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	Increasing survival will have a positive impact on those connected to the patient.

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 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?	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. It will reduce both risk of relapse and improve overall survival. These improved long term outcomeswill have a very positive effect on health related benefits.
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?	The side effect profile of Osimertinib is generally favourable when compared to conventional cytotoxic chemotherapy. Most toxicities are low grade and the oncology community has significant experience in managing these appropriately as TKI's have been used in more advanced disease settings for many years. It is relatively rare to have to stop treatment as the majority of side effects improve with a dose reduction.
20. Do the clinical trials on the 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 light subsequently?	Yes the trial comparator arm mirrors standard practice prior to availability within the CDF of this technology. Overall survival, Disease free survival and intracranial relapse free survival and Health related Quality of life are the most important outcomes and all were measured within the ADAURA trial. I am unaware of any additional adverse effects.

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?	There is little published real world data in the adjuvant setting. I understand data on the UK experience is due to be presented at the forthcoming British Thoracic Oncology Group meeting however this is not currently in the public domain. I also do not have access to data from the CDF. A Chinese study – the ADDRESS study looked more at uptake of treatment rather than efficacy and tolerability and concluded more patients should be offered treatment. Data from Canada has been published: Evaluation of Cost-Effectiveness Of Osimertinib in patients with resected EGFR mutation -positive NSCLC. Andre Verhoek et al PharmacoEconnomics-Open(2023) 7;455-467 The study which used some real world data to inform the modelling concluded that the use of adjuvant Osimertinib was cost effective compared to active surveillance after standard of care treatment but again does not report toxicity or efficacy. When Osimertinib has been used in more advanced cancer settings, benefit and toxicity has been similar to that seen in clinical trials.
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 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	It is recognised that certain cultural groups access healthcare e.g. lung cancer screening programmes less than others. This may be a barrier to initial surgery however once a patient is being managed by a multidisciplinary team, I do not foresee any equality issues with regard to the adjuvant phase of treatment

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.	
Use of Osimertinib during period of the managed access agreement (MAA)	
24. Are there any important outcome data that were not collected during the managed access period?	From a patient's perspective grade 1 and 2 toxicities can be challenging and potentially lead to compliance issues. To my knowledge these have not formally been collected but would form part of the patients on treatment review.
25. Do you have experience of administering the technology during the period of the MAA? If yes: • Please outline your experience • Did any people decline treatment? What were their reasons why?	Yes I have treated a small number of patients. All bar one remain on treatment with no evidence of relapse and very manageable toxicity profiles. Two patients declined the cytotoxic component of the potential adjuvant treatment as they were slowly recovering from surgery.

• What has been the experience of on treatment monitoring and managed access assessments	The patient who stopped had an unrelated medical event with a significant decline in performance status such that continuing an adjuvant therapy was felt inappropriate. One patient declined treatment simply because she did not wish to take tablets daily and need to have ongoing regular engagement with hospital services. I work along a nurse prescriber who meets the patient for a first day talk, concomitant medicines check etc. She then monitors the patient and their blood and ECG results. The majority of the toxicity assessments are telephone appointments. I will then see the patient face to face for any scan results. The experience has been similar to my use of the drug in more advanced settings with patients remaining well.
26. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring	No
27. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	It is important that multidisciplinary teams ensure that genetic testing for EGFR is performed as reflex test and the result available prior to the initial treatment decision being made. This is important for a number of reasons 1) Some patients may be choosing whether to undergo surgery +/- adjuvant therapy or radical chemoradiotherapy +/- Durvalumab 2) It is important that patients appreciate that adjuvant therapy is part of their planned treatment rather than this being a surprise to them when they receive their results from the surgeons. 3) The timelines within the MAA scheme were quite rigid meaning that treatment decisions may have been rushed between the patient and the oncologist and subsequent availability of new patient assessments in chemotherapy units. Certain areas of the country have significant delays in final pathology being available including genomics resulting in the first follow up by the surgeon either being delayed or performed prior to the

	referring MDT having the full results with which to advise adjuvant therapies. 4) It is important that the thoracic surgeons are aware of the referral criteria which differ from those for adjuvant cytotoxic chemotherapy with regard to stage. 5) Patients derive great benefit from linking in to support networks such as the EGFR Positive UK charity

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.

Adjuvant Osimertinib significantly extends disease free and overall survival which is vital for this patient population.

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.

Adjuvant Osimertinib +/- 4 cycles of platinum doublet chemotherapy should be recommended for use in the adjuvant treatment of EGFR mutation positive NSCLC for >/= Stage 1B resected disease.

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Clinical expert statement

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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 **12 April 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Part 1: Treating EGFR mutation-positive non-small-cell lung cancer (NSCLC) after complete tumour resection and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Eric Lim
2. Name of organisation	Royal Brompton Hospital
3. Job title or position	Professor of thoracic surgery
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 NSCLC after complete tumour resection? ☒ A specialist in the clinical evidence base for EGFR mutation-positive NSCLC after complete tumour resection? ☐ 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 organisation's submission)	☒ 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.)
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

Clinical expert statement

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for EGFR mutation-positive NSCLC after complete tumour resection? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve length and quality of life (this include reduction of recurrence which impacts on patients quality of life).
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)	Improvement in survival by 20%, reduction of recurrence by 20%.
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR mutation-positive NSCLC after complete tumour resection?	Yes, currently Osimertinib is the only licenced preventative treatment
11. How is EGFR mutation-positive NSCLC after complete tumour resection 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?	Tumours more than 4cm or node positive are eligible to receive Osimertinib for three years. It shouldn't vary amongst professionals.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it is currently in use as recommended.

• 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)	
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, to both questions.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Most effective in Ex-19del and L858R mutation subsets, perhaps less effective in uncommon EGFR mutations
15. 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)	It is easy to use, and well tolerated in general, but will require oncology follow up to screen for adverse effects.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Currently stopped for progression or three years, without requirement for additional testing.
17. 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? • 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	Yes, it includes very practical benefits such as spending more time with family outside of hospital visits due to reduction in recurrence.
18. 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? • 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?	It is a step change as it has very high magnitude of effect.
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?	Rash is most common.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	Yes

• 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 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?	It broadly mirrors that of the clinical trial
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 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	Non-smoking Chinese women are the subgroup that is likely to benefit the most. We need to ensure there is no language or cultural barrier to access.

• 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.	
Use of Osimertinib during period of the managed access agreement (MAA)	
24. Are there any important outcome data that were not collected during the managed access period?	No
25. Do you have experience of administering the technology during the period of the MAA? If yes: • Please outline your experience • Did any people decline treatment? What were their reasons why? • What has been the experience of on treatment monitoring and managed access assessments	No
26. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring	No
27. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	After prescription is stopped at 3 years, there is likely to be a rebound in recurrence, we need to consider longer prescribing periods for example in advanced disease.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Highly efficacious treatment

Will improve survival and reduce recurrence

Need to consider longer prescribing period after 3 years

Click or tap here to enter text.

Click or tap here to enter text.

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Single Technology Appraisal

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

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 or caring for someone with EGFR mutation-positive non-small-cell lung cancer (NSCLC) after complete tumour resection. 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).

NICE National Institute for Health and Care Excellence

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 **12 April 2024.** 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 adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

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Part 1: Living with this condition or caring for a patient with EGFR mutation-positive NSCLC after complete tumour resection

Table 1 About you, NSCLC, current treatments and equality

1. Your name	Gini Harrison
2. Are you (please tick all that apply)	☐ A patient with EGFR mutation-positive NSCLC after complete tumour resection? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with EGFR mutation-positive NSCLC after complete tumour resection? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
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
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, or caring for someone with, EGFR mutation-positive NSCLC after complete tumour resection?	In December 2021, whilst on maternity leave and after experiencing shoulder pain for 10 months that was put down to bad breastfeeding posture, I had an MRI that revealed a tumour in the apex of my right lung, and another in my scapular. Shortly after this, a biopsy revealed it to be EGFR+ NSCLC. After being treated with curative intent chemoradiation, I became a trustee for EGFR+ UK, where I work with and advocate for patients – including those who have had complete tumour resection. I am also a Professor of Psychology and have recently been carrying out research with EGFR patients, exploring their wellbeing needs.
7a. What do you think of the current treatments and care available for EGFR mutation-positive NSCLC after complete tumour resection on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Care following resection seems to be very varied. While some patients are offered some form of systemic therapy following surgery, this isn't always the case. And when adjuvant therapy is offered, it is often some form of platinum-based doublet chemotherapy (or sometimes, and older generation of TKI).

	Doing nothing after surgery can often leave patients feeling like they are “just waiting for the other shoe to drop”. They have a constant fear of recurrence, which can significantly impact their lives. On the other hand, the physical and psychological impact of adjuvant chemotherapy can be huge. Our EGFR members often report struggling with the side effects of the drugs, which can have a huge negative impact on their quality of life. Having to live around schedules of chemo infusions and side-effects can feel very limiting, and can significantly negatively impact their wellbeing. These views broadly represent those of the < 700 members of EGFR+ UK.
8. If there are disadvantages for patients of current NHS treatments for EGFR mutation-positive NSCLC after complete tumour resection (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As stated above, the experience of doing nothing after a cancer diagnosis can lead patients to experience significant anxiety and panic. Alternatively, the side effects of adjuvant chemo can often be brutal. Our members have described a whole host of negative side effects following chemo including: fatigue, nausea, vomiting, constipation, diarrhoea, muscle aches, cognitive dysfunction (including memory and attention issues), constant illness, and neutropenia. As well as the side effects, the scheduling around IV infusions is logistically limiting, and can also negatively impact quality of life. Furthermore, chemotherapy may not have satisfactory brain penetration – this is problematic, as brain metastases are common in EGFR+ lung cancer, and is something patients often worry about. EGFR patients are younger than the average lung cancer patients. They were often fit and healthy before diagnosis, and many have young families. Having to go through a

	chemo regime that interrupts their lives has a huge detrimental effect on their wellbeing and ability to function more broadly. While I haven't had a resection myself, these are all experiences that I have had with my own treatment – and they are very difficult to take.
9a. If there are advantages of osimertinib 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 osimertinib 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**	9a.) The side effects of Osimertinib as well documented to be significantly less than chemo (and indeed, older generation TKIs). Treatment-related adverse events are fewer and less extreme with chemo, meaning Osimertinib is less likely to have a negative impact on quality of life. Another huge advantage is that while chemo involves hospital visits and infusions (which literally take hours), Osimertinib involves simply taking a daily tablet at home. Less time in hospitals, which allows patients to live more normally, and not have to be reminded of their status as a 'cancer patient'. Ultimately, this mean patients will be able to engage more fully and function better in their lives. Taking a drug with a good safety profile, that has been repeatedly shown to be effective in treating EGFR cancer (like Osimertinib), can also help patients to feel like they are doing all that they can to stay well. This can help to give patients a sense of control over their health, which can have a positive impact on their wellbeing. 9b.) – I think they are all equally important for their impact on quality of life. 9c.) – Yes! As stated above, Osimertinib has fewer side effects, and can be taken at home. It gives the patient an option of a drug to take beyond chemo, that would allow them to stay at home for their treatment and live relatively normally while taking it. These things are invaluable when it comes to wellbeing and quality of life.

	Furthermore, there is good evidence the Osimertinib penetrates the brain, and can keep brain mets under control.
10. If there are disadvantages of osimertinib over current treatments on the NHS please describe these. For example, are there any risks with osimertinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am unsure of the implications of future access to Osimertinib if it prescribed after resection. For example, if a patient was prescribed it for a limited take after surgery (say 2-3 years) and then stopped treatment. If they had recurrence may years later, would its initial use preclude them from being able to access it again (i.e. rechallenge)? If so, this might be a disadvantage. Continued use of Osimertinib after 3 years is not recommended – would this be the case in this setting too? If so, what would happen after those 3 years? If Osimertinib is prescribed in the adjuvant setting it may not be available as a later treatment / re-challenge Many of the members of the EGFR patient group have been on more than one TKI and the general consensus is that Osimertinib has fewer and less extreme side effects that the older generation TKIs. I have no personal experience of taking Osimertinib
11. Are there any groups of patients who might benefit more from osimertinib 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	Taking a single daily tablet is easier for anyone to incorporate into their daily routine. However, as Osimertinib is less likely to impact the immune system than chemo, it would also be beneficial for patients who are regularly exposed to viruses/illnesses. For example, I have two small children and when I was going through chemotherapy, I was constantly in A&E due to the illnesses I had caught from them. Being able to take a drug that had a lesser impact on immunity would have been hugely preferable! Hospital visits are difficult for anyone, but are especially difficult for those patients who are particularly frail, or who have mobility or cognitive issues. As such, these patient groups may also benefit more from the flexibility associated with 3rd gen TKIs.

12. Are there any potential equality issues that should be taken into account when considering NSCLC and osimertinib? 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 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.	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 EGFR patients have reported in Section 7). 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.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Patients' greatest fear following resection is recurrence. Osimertinib gives patients protection against recurrence, and gives them a sense of control over their health.
- Taking a daily TKI has minimal impact on the patient or their family and enables the patient to live a full and active life.
- The side effects of Osimertinib are minimal in comparison to chemotherapy.
- Osimertinib can offer protection against brain metastases.
- Overall, taking Osimertinib after resection is likely to have a positive impact on patients' wellbeing and quality of life over current options (e.g. doing nothing, or having adjuvant chemo).

Thank you for your time.

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Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (review of TA761) [ID5120]

External Assessment Group Report

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
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Date completed	28th March 2024 (post-FAC version)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136233.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Dr Laura Cove Smith, The Christie NHS Foundation Trust, and Dr Robin Young, Sheffield Teaching Hospitals NHS Foundation Trust, for clinical advice relating to this project. We would also like to thank Dr Aline Navega Biz, Research Fellow, SCHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, SCHARR, for providing administrative support and for preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Tappenden P, Poku E, Ren S, Yee M, Nalbant G, Clowes M. Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (review of TA761) [ID5120]. External Assessment Group Report. Sheffield Centre for Health and Related Research, 2024.

Contributions of authors

Paul Tappenden acted as the EAG lead. Mark Clowes critiqued the company's search strategy. Edith Poku and Gamze Nalbant summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Sarah Ren critically appraised the statistical aspects of the submission and undertook additional survival analyses. Paul Tappenden and Mon Mon Yee summarised and critically appraised the health economic analysis submitted by the company and undertook additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

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Abbreviations

ABCP	Atezolizumab, bevacizumab, carboplatin and paclitaxel
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
AM	Active monitoring
ASA	Additional sensitivity analysis
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CMU	Commercial Medicines Unit
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DF	Disease-free
DFS	Disease-free survival
DG	Diagnostics Guidance
DM1	First-line treatment for distant metastases
DM2	Second-line treatment for distant metastases
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EA	Exploratory analysis
EAG	External Assessment Group
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor mutation-positive
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of treatment
EQ-5D	Euroqol 5-Dimensions
EQ-5D-3L	Euroqol 5-Dimensions 3-Level
ERG	Evidence Review Group
Ex19del	Exon 19 deletion
FAD	Final Appraisal Determination
FAS	Full analysis set
GLS	Generalised least squares
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HODaR	Health Outcomes Data Repository

HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IDMC	Independent Data Monitoring Committee
ILD	Interstitial lung disease
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LRR	Loco-regional recurrence
LVEF	Left ventricular ejection fraction
LYG	Life year gained
MAA	Managed Access Agreement
MCM	Mixture-cure model
MCS	Mental component score
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MSE	Mean squared error
N	Number
N/a	Not applicable
NC	Not calculated
NCPE	National Centre for Pharmacoeconomics
NG	NICE Guideline
NGS	Next-generation sequencing
NHS	National Health Service
NHSE	NHS England
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
OS	Overall survival
Osi	Osimertinib
PAS	Patient Access Scheme
PCS	Physical component score
PDC	Platinum doublet chemotherapy
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research unit
QALY	Quality-adjusted life year
QTc	Corrected QT
RCR	Royal College of Radiologists
RCS	Restricted cubic spline
RCT	Randomised controlled trial

RDI	Relative dose intensity
RMME	Repeated measures mixed effect
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCAR	Severe cutaneous adverse reaction
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SJS	Stevens-Johnson syndrome
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STM	State transition model
TA	Technology appraisal
TEN	Toxic epidermal necrolysis
TKI	Tyrosine kinase inhibitor
TNM	Tumour Node Metastasis
TP	Transition probability
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States
WHO	World Health Organization
WTP	Willingness-to-pay

1. EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses osimertinib as adjuvant treatment following complete tumour resection in adults with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations. This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 outlines the key model outcomes and the modelling assumptions that have the greatest effect of the ICER. Sections 1.3 to 1.5 summarise the decision problem and the evidence and explain the key issues in more detail. The results of the EAG's preferred analyses and additional sensitivity analyses are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues is detailed in the main EAG report.

All issues identified represent the EAG's view, not necessarily the opinion of the National Institute for Health and Clinical Excellence (NICE).

1.1 Overview of the EAG's key issues

The company's submission (CS) includes a systematic literature review (SLR) of studies of osimertinib for the adjuvant treatment of adults with stage IB-IIIA EGFR mutation-positive (EGFRm) NSCLC after complete tumour resection. The company's economic model assesses the cost-effectiveness of adjuvant osimertinib versus active monitoring within this same population, informed by the ADAURA randomised controlled trial (RCT) and external data. The key issues identified by the EAG are summarised in Table 1.

Table 1: Summary of the EAG's key issues

ID5120	Summary of issue	Report sections
Issue 1	Uncertainty around long-term DFS and OS outcomes for adjuvant osimertinib, including potential curative effects	5.3.6 (critical appraisal point 3, with related discussion around survival analysis and cure assumptions under point 4 and point 5)
Issue 2	Uncertainty around the use of osimertinib in the first-line metastatic setting (as re-treatment and as treatment for relapsed active monitoring patients)	5.3.6 (critical appraisal point 6)

DFS - disease-free survival; OS - overall survival

The company's economic model includes an assumption of cure for both the adjuvant osimertinib and active monitoring groups. The EAG's preferred analyses are presented as optimistic and pessimistic

scenarios around the cure assumptions for the adjuvant osimertinib group in the company's model. The EAG's preferred optimistic scenario retains the cure assumptions applied in the company's model. In this scenario, the model applies a "cure proportion" after 5 years in patients receiving active monitoring, and after 8 years in patients receiving adjuvant osimertinib, with a preceding "warm-up" phase starting after 4 years in both groups. During this warm-up phase, the cure proportion increases approximately linearly from 0% to 95% by the final cure timepoint. This is applied in the model as a percentage reduction in the predicted probability of experiencing loco-regional or distant recurrence estimated from parametric survival models fitted to time-to-event data for these events. The EAG's preferred pessimistic scenario retains the 5- and 8-year final cure timepoints, but removes the warm-up period from both treatment groups. Under the EAG's optimistic scenario, the model predicts that adjuvant osimertinib will lead to a sustained benefit in disease-free survival (DFS) and overall survival (OS) during the extrapolation period of the model. Under the EAG's pessimistic scenario, the model predicts that the DFS function for adjuvant osimertinib and active monitoring intersect at approximately 8 years (i.e., there is no sustained benefit).

The EAG's preferred optimistic and pessimistic analyses also include: the correction of minor model errors; the application of slightly different utility values; the extension of disease management costs for all non-relapsed patients up to the final cure timepoints, and the estimation of drug wastage costs for all tyrosine kinase inhibitors (TKIs) including osimertinib.

1.2 Overview of the key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Compared with active monitoring alone, the company's model indicates that adjuvant osimertinib impacts on QALYs by:

- Reducing the probability of experiencing of loco-regional and distant (metastatic) recurrence, ultimately leading to a higher proportion of patients being cured.
- Extending overall survival (OS) as a consequence of improved DFS.
- Increasing QALY losses associated with adverse events (AEs).

The company's model suggests that adjuvant osimertinib affects costs by:

- Increasing the costs of adjuvant treatment for patients who are disease-free.
- Reducing the expected costs of treating loco-regional and distant recurrence by reducing the risk of these events.

The modelling assumptions that have the greatest effect on the ICER are:

- The cure timepoints applied to patients who remain disease-free following adjuvant osimertinib or active monitoring, and whether the assumed warm-up period is included in the model.
- The parametric survival models used to predict the risks of experiencing loco-regional recurrence and distant recurrence (denoted "TP1" and "TP2", respectively).
- The proportion of patients who are assumed to receive first-line treatment with osimertinib following distant recurrence (as re-treatment in the adjuvant osimertinib group, and as initial therapy for relapsed active monitoring patients).

1.3 The decision problem: Summary of the EAG's key issues

In NICE TA761, osimertinib was recommended for use within the Cancer Drugs Fund (CDF) as adjuvant treatment after complete tumour resection in adults with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The company's proposed positioning of osimertinib in routine commissioning is in line with its full marking authorisation for the adjuvant therapy indication. The decision problem addressed in the CS is partly in line with the final NICE scope. The CS compares adjuvant osimertinib against active surveillance. The final NICE scope also lists (adjuvant) platinum-based chemotherapy as a comparator; however, the CS argues that chemotherapy is not a relevant comparator, and no comparison has been made between adjuvant osimertinib and adjuvant chemotherapy. The EAG's clinical advisors agreed that chemotherapy is not a relevant comparator. The EAG notes that it is unclear how a reliable indirect treatment comparison (ITC) between adjuvant osimertinib and adjuvant chemotherapy could have been conducted. The final NICE scope includes the consideration of subgroups defined according to disease stage, where evidence allows. The CS contains clinical subgroup analyses of DFS and OS outcomes across a range of patient characteristics, including disease stage. However, the CS does not present cost-effectiveness analyses of adjuvant osimertinib within individual subgroups. This means that heterogeneity cannot be explored.

1.4 The clinical effectiveness evidence: Summary of the EAG's key issues

The main clinical evidence presented in the CS is the ADAURA Phase III, multicentre, randomised controlled trial (RCT). Within this trial, 682 patients with completely resected stage IB-IIIA EGFR mutation-positive NSCLC were randomised to receive adjuvant osimertinib or placebo for 3 years. Approximately 60% of patients had received prior adjuvant chemotherapy. The primary efficacy endpoint in ADAURA was DFS in the stage II-IIIA subgroup, although the CS states that the main population of relevance for this appraisal is the overall population in ADAURA, which includes patients with stage IB to IIIA EGFR NSCLC. The evidence presented in the CS reflects data cut-offs (DCOs) of the 11th April 2022 for DFS and the 27th January 2023 for OS. Data for these endpoints have been updated since TA761.

The updated efficacy analyses suggest that compared with placebo, adjuvant osimertinib provides statistically significant benefits in DFS and OS, regardless of prior adjuvant chemotherapy use. Efficacy outcomes were generally consistent for the overall population and the stage II-IIIA subgroup. In the overall population, the latest DCO from ADAURA suggests that osimertinib improves DFS (hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.21, 0.34, *p*=not reported [NR]) and central nervous system (CNS) DFS (HR 0.36; 95% CI 0.23, 0.57, *p*=NR). Compared with placebo, osimertinib led to fewer distant recurrences and fewer CNS recurrences. Data on OS were immature and median OS was not reached in either trial arm. Compared with placebo, osimertinib led to a statistically significant reduction in the risk of death (HR 0.49; 95% CI 0.34, 0.70, $p<0.0001$) in the overall population. Subgroup analyses suggest that the relative treatment effect for DFS remains generally consistent, regardless of prior chemotherapy use. Limited data on health-related quality of life (HRQoL) are presented in the CS. In the overall population, 11% of patients had treatment-related Grade≥3 AEs in the osimertinib group compared with 2% in the placebo group.

The CS presents additional data collected with the Systematic Anti-Cancer Therapy (SACT) dataset relating to 143 patients who have received adjuvant osimertinib in England. Median OS was not reached within the SACT population. Median treatment duration in SACT was shorter than in ADAURA (14.7 months versus 35.8 months), but this is due to 80% of patients in SACT still receiving treatment at the time of the DCO for the analysis. No data on re-treatment rates are available from SACT.

The EAG notes that despite the availability of additional data from ADAURA, long-term DFS and OS outcomes in patients treated with adjuvant osimertinib, including the potential for cure, remain uncertain. The CS states that no further data on recurrence are being collected in ADAURA.

1.5 The cost-effectiveness evidence: Summary of the EAG's key issues

The company's economic model assesses the cost-effectiveness of adjuvant osimertinib versus active monitoring for the treatment of adults with fully resected stage IB-IIIA EGFRm NSCLC over a lifetime horizon from the perspective of NHS and Personal Social Services (PSS). The model uses a semi-Markov state transition approach including five health states: (i) disease-free (DF); (ii) loco-regional recurrence (LRR); (iii) first-line treatment for distant metastases (DM1); (iv) second-line treatment for distant metastases (DM2) and (v) dead. Caregiver effects are not included. Health outcomes and costs are discounted at a rate of 3.5% per annum in the base case analysis. As noted in Section 1.3, no subgroup analyses are presented, and adjuvant chemotherapy is not considered as a comparator.

The company's economic model for the current appraisal is generally similar to the earlier model used to inform TA761. The model uses the latest DCOs of DFS and OS from ADAURA to estimate time-dependent risks of loco-regional recurrence and distant metastases for patients who are disease-free.

Clinical outcomes for patients with relapsed disease are informed by external data from the CancerLinQ database, the FLAURA RCT, the IMPower150 RCT and general population life tables. No excess mortality risk is considered for patients who remain disease-free. The model includes structural assumptions of cure for patients who remain disease-free at 5 years in the active monitoring group and at 8 years in the adjuvant osimertinib group, as described in Section 1.1. Health state utility values are based on data from ADAURA, FLAURA and the literature. Resource costs were informed by ADAURA, previous NICE appraisals, standard costing sources, literature, and assumptions. The model includes a Patient Access Scheme (PAS) discount for osimertinib of [redacted]. The model assumes that 50% of patients in the adjuvant osimertinib group who experience distant relapse after 4 years are re-treated with osimertinib as first-line therapy; this was a key area of uncertainty in TA761 and this assumption has not been updated in the company's current model. Overall, the model suggests that compared with active monitoring, adjuvant osimertinib: (i) increases DFS; (ii) extends OS (as a consequence of improved DFS and the structural cure assumptions); (iii) increases adjuvant treatment costs, and (iv) reduces downstream treatment costs, largely as a consequence of fewer patients experiencing relapse.

Following the clarification round, the company submitted two updated versions of their economic model. The probabilistic version of the company's second updated model suggests that the ICER for adjuvant osimertinib versus active monitoring is £16,485 per QALY gained. The deterministic ICER is similar at £15,656 per QALY gained.

The EAG's preferred optimistic and pessimistic analyses include error corrections and minor alterations to utility values and costs assumptions. The EAG's preferred optimistic analysis retains the company's cure timepoints of 5 years for active monitoring and 8 years for adjuvant osimertinib, including the warm-up period starting after 4 years in both treatment groups. The EAG's pessimistic scenario analysis retains the final cure timepoints, but removes the warm-up period. Under the optimistic scenario, the probabilistic version of the model leads to an ICER of £16,991 per QALY gained. The deterministic ICER is similar, at £17,156 per QALY gained. Under the pessimistic scenario, the probabilistic version of the model leads to an ICER of £45,677 per QALY gained. The deterministic ICER for the pessimistic scenario is noticeably higher, at £51,952 per QALY gained.

The EAG has two main concerns regarding the company's model. These relate to: (i) uncertainty around long-term DFS and OS outcomes for patients receiving adjuvant osimertinib, including potential curative effects (Issue 1), and (ii) uncertainty around the use of osimertinib in the first-line metastatic setting (in both the adjuvant osimertinib and active monitoring groups [Issue 2]). These issues are summarised below. The EAG's critical appraisal of the company's model includes discussion around a wider set of issues, including concerns regarding the company's parametric survival model fitting and selection approaches, the unconventional approach to modelling cure applied within the model, and the

calibration approach used to force model-predicted OS to better align with the OS observed in ADAURA. However, these issues are each related to uncertainty around the long-term DFS and OS for adjuvant osimertinib and, as such, they are not discussed separately within this summary.

Issue 1: Uncertainty around long-term DFS and OS outcomes for adjuvant osimertinib, including potential curative effects

Report section	5.3.6 (critical appraisal point 3, with related discussion around survival analysis and cure assumptions under point 4 and point 5)
Description of issue and why the EAG has identified it as important	Longer-term data on DFS and OS from ADAURA have become available since TA761. These updated data suggest treatment benefits which favour osimertinib over placebo on both endpoints. However, there remains uncertainty around whether the treatment advantage for osimertinib indicated by the Kaplan-Meier plots of DFS and OS will persist in the longer-term. There is also uncertainty around the curative potential of adjuvant osimertinib - although a plateau in DFS is expected for adjuvant osimertinib, this is not evident from the observed DFS data from ADAURA. The company's economic model suggests a sustained gap in both DFS and OS favouring adjuvant osimertinib versus active monitoring. This model prediction is strongly influenced by structural cure assumptions applied by the company, which are highly uncertain. In order to explore this uncertainty, the EAG undertook additional analyses and sought further input from their clinical advisors: • The EAG replicated the pseudo individual patient data (IPD) from ADAURA and plotted the empirical (smoothed) hazard for both treatment groups. These analyses indicate that the DFS hazard for the placebo group is decreasing over time and becomes very low within the observed period of the trial. This provides some support for an assumption of cure in a proportion of people receiving active monitoring. In contrast, the DFS hazard in the adjuvant osimertinib group is increasing over time. The available data from ADAURA, which includes a maximum follow-up for DFS of approximately 6 years, does not provide supportive evidence for a cure assumption in the adjuvant osimertinib group. The EAG notes that the cure warm-up period applied in the company's economic model leads to a turning point in the modelled osimertinib DFS hazard which deviates from the DFS hazard that has been observed in the osimertinib group of the trial. • Using these same data from ADAURA, the EAG generated a plot of the time-varying HR for DFS for adjuvant osimertinib versus placebo. This plot indicates that the relative treatment effect on DFS for adjuvant osimertinib versus placebo is increasing (worsening) over time. If the trend in the observed data were to continue in the longer-term, the gap between the DFS curves would diminish and the curve for the osimertinib group may catch up with the curve for the placebo group. • The EAG fitted mixture-cure models (MCMs) to the replicated DFS data from ADAURA to explore whether cure fractions could be estimated, and if so, whether these are consistent across alternative models. The EAG was able to fit MCMs to the placebo group data; these gave broadly consistent cure fractions of 23% to 32% across all six MCMs fitted. This may provide some support for an assumption of cure in the active monitoring group. Conversely, the EAG was able to fit only two of six MCMs to the data for the adjuvant osimertinib group in ADAURA. This does not mean that osimertinib is not curative, but it does suggest that the available data from ADAURA are not sufficiently mature to support an assumption of cure. • The EAG sought additional input from two clinical advisors regarding the predictions of DFS and OS generated by the company's model. One of the

	EAG's clinical advisors considered the company's DFS and OS projections to be clinically plausible, but commented that long-term outcomes following 3-year discontinuation of treatment were highly uncertain. The second clinical advisor was unsure whether the gaps in DFS and OS predicted by the company's model would be sustained in the longer-term. They stated that it was plausible that there may be a sustained gap which is smaller than that predicted by the company's model. They also mentioned the possibility that the osimertinib DFS function might catch up with the placebo DFS function.
What alternative approach has the EAG suggested?	Owing to the uncertainty around long-term effects on DFS and OS, the EAG's exploratory analyses using the company's economic model are presented for optimistic and pessimistic scenarios (denoted "EA6" and "EA7", respectively). Both the optimistic and pessimistic scenarios assume a final cure timepoint of 5 years for active monitoring and 8 years for adjuvant osimertinib. The optimistic and pessimistic scenarios differ as follows: • The EAG's optimistic scenario retains the company's warm-up assumptions, whereby the "cure proportion" (the percentage reduction in the predicted DFS risk from the parametric survival models for DFS events) is assumed to increase approximately linearly from the end of year 4 until the final cure timepoint in each treatment group. Applying these assumptions within the model leads to a sustained gap between the treatment groups in DFS and OS over time. • The EAG's pessimistic scenario removes the warm-up period altogether but retains the company's assumed final cure timepoints. Applying these assumptions within the model leads to the modelled DFS curve for adjuvant osimertinib catching up with the modelled DFS curve for active monitoring at approximately 8 years. The EAG undertook additional sensitivity analyses across both optimistic and pessimistic scenarios. A "middle-ground" scenario – "ASA1a" – was undertaken whereby the final cure timepoint for the adjuvant osimertinib group was set equal to 7 years (with no warm-up period). This analysis suggests a smaller gap in DFS and OS compared with the EAG's optimistic scenario and the company's base case model.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred optimistic scenario (EA6) suggests that the probabilistic ICER for adjuvant osimertinib versus active monitoring is £16,991 per QALY gained. The deterministic ICER is similar, at £17,156 per QALY gained. The EAG's preferred pessimistic scenario (EA7) suggests that the probabilistic ICER for adjuvant osimertinib versus active monitoring is £45,677 per QALY gained. The deterministic ICER is higher, at £51,952 per QALY gained. The EAG's "middle-ground" scenario (ASA1a) suggests a deterministic ICER of £27,611 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	[redacted] The EAG understands that the ADAURA trial has been unblinded and no further data on recurrence are being collected.

Issue 2: Uncertainty around the use of osimertinib in the first-line metastatic setting

Report section	5.3.6 (critical appraisal point 6)
Description of issue and why the EAG has identified it as important	The company's model assumes that amongst patients who receive adjuvant osimertinib and subsequently develop distant metastases after 4 years, 50% will go on to receive osimertinib as first-line treatment in the metastatic setting. The CS highlights that the proportion of patients who would be re-treated with osimertinib is unknown and there are no clinical studies of osimertinib in patients with metastatic disease who have previously received adjuvant osimertinib. The EAG's clinical advisors suggested that the vast majority of patients who relapse following adjuvant osimertinib would be re-treated with osimertinib in the first-line metastatic setting. The CS does not provide any new evidence on re-treatment rates and as such, this aspect of the model remains highly uncertain. The EAG notes that the re-treatment probability had little impact on the company's base case ICER in TA761 because the cure timepoint coincided with the re-treatment timepoint (both occurring at 5 years). However, in the current appraisal, the final cure timepoint for the adjuvant osimertinib group has been moved to 8 years and the re-treatment timepoint has been moved to 4 years; consequently, assumptions about the re-treatment probability now have a greater effect on the ICER. The company's model also assumes that in the active monitoring group, 83% of patients who experience distant recurrence receive osimertinib as first-line treatment for metastatic disease. This estimate is based on 2023 Ipsos market share data on TKIs used in the first-line setting for EGFRm NSCLC. The EAG's clinical advisors suggested that this proportion would likely to be higher than 83%. The EAG notes that the Ipsos market share data do not specifically relate to patients who were eligible for treatment with osimertinib (those with a performance status of 0 or 1), and that other TKIs such as gefitinib may be offered to patients who are less fit at the point of relapse.
What alternative approach has the EAG suggested?	The EAG conducted additional sensitivity analyses exploring the impact of increasing the proportion of patients treated with osimertinib in the first-line metastatic setting. Separate analyses were undertaken exploring the impact of assuming that 60%, 70% or 80% of patients in the adjuvant osimertinib group are re-treated with osimertinib following distant recurrence (ASA3a-c). A fourth scenario analysis was conducted to explore the impact of assuming that all patients with distant recurrence are treated with osimertinib as first-line treatment for metastatic disease (ASA3d).
What is the expected effect on the cost-effectiveness estimates?	Increasing the re-treatment percentage from 60% to 80% leads to ICERs ranging from £19,369 to £24,184 per QALY gained under the optimistic scenario, and from £54,978 to £61,636 per QALY gained under the pessimistic scenario (ASA3a-c). When all patients with distant recurrence are assumed to be treated with first-line osimertinib, the ICER for the optimistic scenario is increased to £26,004 per QALY gained and the ICER for the pessimistic scenario is increased to £66,961 per QALY gained (ASA3d).
What additional evidence or analyses might help to resolve this key issue?	Further evidence is required on the proportion of patients who are re-treated with osimertinib following distant recurrence. Further evidence is also required on the proportion of patients who receive active monitoring, experience metastatic relapse and go on to receive an alternative TKI as first-line therapy, despite being eligible for osimertinib. In the absence of these data, assumptions will be necessary.

1.6 Summary of EAG's preferred model results

The results of the EAG's preferred analyses are summarised in Table 2. EA6 and EA7 reflect the EAG's preferred optimistic and pessimistic scenarios, respectively. Results are presented separately using the probabilistic and deterministic versions of the models. The results of the EAG's additional sensitivity analyses (ASAs) are presented in Table 3.

Modelling errors identified by the EAG are described in Section 5.3.6. For further details of the exploratory and sensitivity analyses undertaken by the EAG, see Section 5.5.

Table 2: Summary of EAG's preferred analysis, including PAS for adjuvant osimertinib

Option	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's second revised base case, deterministic	[redacted]	[redacted]	[redacted]	**£15,656**
Company's second revised base case, probabilistic	[redacted]	[redacted]	[redacted]	**£16,485**
EA1: Correction of remaining model errors	[redacted]	[redacted]	[redacted]	£15,259
EA2: Using Hernández Alava *et al.* to cap DF/LRR utility values and for age-adjustment	[redacted]	[redacted]	[redacted]	£14,937
EA3: All patients incur disease management costs in the DF state until the final cure time point	[redacted]	[redacted]	[redacted]	£17,198
EA4: Inclusion of wastage costs for osimertinib and early TKIs	[redacted]	[redacted]	[redacted]	£15,586
EA5: No warm-up period in either group, patients cured at 8 years in the adjuvant osimertinib group and at 5 years in the active monitoring arm	[redacted]	[redacted]	[redacted]	£51,452
EA6a: EAG-preferred optimistic analysis (EA1-4 combined), deterministic	[redacted]	[redacted]	[redacted]	**£17,156**
EA7a: EAG-preferred pessimistic analysis (EA1-5 combined), deterministic	[redacted]	[redacted]	[redacted]	**£51,952**
EA6b: EAG-preferred optimistic analysis (EA1-4 combined), probabilistic	[redacted]	[redacted]	[redacted]	**£16,991**
EA7b: EAG-preferred pessimistic analysis (EA1-5 combined), probabilistic	[redacted]	[redacted]	[redacted]	**£45,677**

EAG - External Assessment Group; EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DF - disease-free; LRR - loco-regional recurrence; TKI - tyrosine kinase inhibitor
** Undiscounted*

Table 3: EAG's additional sensitivity analysis results, including PAS for adjuvant osimertinib, deterministic

Additional sensitivity analysis	Optimistic scenario – cure at 5 years for active monitoring and 8 years for adjuvant osimertinib, includes warm-up period after 4 years				Pessimistic scenario – cure at 5 years for active monitoring and 8 years for adjuvant osimertinib, excludes warm-up period			
	Inc. LYGs*	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**ICER**
EAG preferred analysis (EA6a/EA7a)	[redacted]	[redacted]	[redacted]	**£17,156**	[redacted]	[redacted]	[redacted]	**£51,952**
ASA1a: Middle ground scenario, EA7a + cure at 7 years for osimertinib and 5 years for active monitoring, no warm-up	Not applicable.				[redacted]	[redacted]	[redacted]	£27,611
ASA1b: Cure proportion for osimertinib equals 1-TTD function + 5 years	Not applicable.				[redacted]	[redacted]	[redacted]	£37,387
ASA2a: TP1 osimertinib: Gompertz model	[redacted]	[redacted]	[redacted]	£28,070	[redacted]	[redacted]	[redacted]	£34,077
ASA2b: TP1 osimertinib: Weibull model	[redacted]	[redacted]	[redacted]	£20,365	[redacted]	[redacted]	[redacted]	£46,897
ASA2c: TP1 osimertinib: Log-logistic model	[redacted]	[redacted]	[redacted]	£18,790	[redacted]	[redacted]	[redacted]	£49,094
ASA2d: TP1 osimertinib: Generalised gamma model	[redacted]	[redacted]	[redacted]	£18,790	[redacted]	[redacted]	[redacted]	£49,094
ASA2e: TP1 AM: Gompertz model	[redacted]	[redacted]	[redacted]	£19,479	[redacted]	[redacted]	[redacted]	£50,970
ASA2f: TP2 osimertinib: Gompertz model	[redacted]	[redacted]	[redacted]	£27,963	[redacted]	[redacted]	[redacted]	£63,074
ASA2g: TP2 osimertinib: Weibull model	[redacted]	[redacted]	[redacted]	£21,054	[redacted]	[redacted]	[redacted]	£54,582
ASA2h: TP2 AM: Weibull model	[redacted]	[redacted]	[redacted]	£17,143	[redacted]	[redacted]	[redacted]	£52,999
ASA3a: 60% re-treated group in osi group	[redacted]	[redacted]	[redacted]	£19,369	[redacted]	[redacted]	[redacted]	£54,978
ASA3b: 70% re-treated group in osi group	[redacted]	[redacted]	[redacted]	£21,716	[redacted]	[redacted]	[redacted]	£58,224
ASA3c: 80% re-treated group in osi group	[redacted]	[redacted]	[redacted]	£24,184	[redacted]	[redacted]	[redacted]	£61,636
ASA3d: 100% of all re-treated patients in osi group and 100% of patients with distant relapse in AM group treated with osi	[redacted]	[redacted]	[redacted]	£26,004	[redacted]	[redacted]	[redacted]	£66,961
ASA4: 34% whole brain RT, 66% stereotactic RT	[redacted]	[redacted]	[redacted]	£17,199	[redacted]	[redacted]	[redacted]	£52,458
ASA5: Re-treatment timepoint = 3 years	[redacted]	[redacted]	[redacted]	£19,491	[redacted]	[redacted]	[redacted]	£53,836
ASA6: Treatment effect for osi in DM1 capped at 5 years	[redacted]	[redacted]	[redacted]	£18,707	[redacted]	[redacted]	[redacted]	£53,378
ASA7: EGFR testing costs included	[redacted]	[redacted]	[redacted]	£18,039	[redacted]	[redacted]	[redacted]	£53,743
ASA8: Utility values from LuCaBIS	[redacted]	[redacted]	[redacted]	£17,269	[redacted]	[redacted]	[redacted]	£47,442

EA - exploratory analysis; ASA - additional sensitivity analysis; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; TP - transition probability; RT - radiotherapy; DM1 - first-line treatment for distant metastasis; EGFR - epidermal growth factor receptor; TTD - time to treatment discontinuation

** Undiscounted*

2. BACKGROUND

This chapter presents a brief summary and critique of the company's description of the disease and the treatment pathways for epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) after complete tumour resection. Section 2.1 summarises and critiques the company's description of the disease. Section 2.2 summarises and critiques the company's overview of the treatment pathway.

2.1 Disease background

2.1.1 Prevalence and epidemiology

Lung cancer is the third most common cancer, with an average of 39,340 new cases per year in England during the period 2016-2018.[1] Lung cancer is the leading cause of cancer mortality in the UK.[1] NSCLC accounts for around 80-85% all lung cancers. The company's submission[2] (CS) states that EGFR mutations are found in between 8% and 16% of patients with early-stage (IB-IIIA) NSCLC, with a higher prevalence seen in younger patients, Asian populations, females and never smokers.[3-7] According to the CS, approximately 50% of EGFR mutations are exon 19 deletions and between 30% and 40% are exon 21 L858R substitutions.[6, 8]

2.1.2 Prognosis

The CS[2] highlights that most patients with early-stage NSCLC can undergo surgical resection with curative intent. Clinical advice received by the company and the External Assessment Group (EAG) supports the view that, without adjuvant osimertinib treatment, patients who do not experience disease relapse within five years of surgery have a very low risk of subsequent recurrence and may be considered functionally cured. However, despite undergoing potentially curative resection, many patients will experience disease recurrence within 5 years of surgery (an estimated 45% with Stage IB, 62% with Stage II, and 76% with Stage III disease).[9] Most relapses which occur following surgery are due to distant recurrence, including brain metastases, although metastases to the lung, bone and liver are also common. Clinical advice received by the company indicates that post-surgical recurrence often occurs rapidly, typically within 18 to 24 months after undergoing the initial surgical resection.[7] The CS states that patients with EGFR mutation-positive (EGFRm) NSCLC have twice the risk of brain metastases compared with patients with wild-type EGFR.[4, 10] The CS also cites literature[10, 11] which suggests that patients with EGFRm NSCLC may have a more severe course of disease and a higher likelihood of distant recurrence compared with patients without these mutations. Once patients experience distant metastasis, there are no available curative treatment options. The CS states that because of a lack of EGFR-targeted treatments for early-stage NSCLC (prior to the availability of

adjuvant osimertinib), there are limited data for overall survival (OS) within this population. However, available data suggest that OS for patients with EGFRm NSCLC who develop brain metastases is less than 18 months from the point of metastatic diagnosis.[4, 12]

2.1.3 Burden of disease

Patients with NSCLC have poorer physical health and lower health-related quality of life (HRQoL) than the general population.[13, 14] The CS[2] highlights that early-stage NSCLC is often asymptomatic for many years. When symptoms arise, they can be wide-ranging and non-specific, including: cough; chest pain; dyspnoea; weight loss; fatigue and bone pain.[15] Patients with EGFRm NSCLC and brain metastases can experience: seizures; speech problems; focal neurological deficits; vision disorder; fatigue; nausea; headaches; memory problems; altered mental status and mobility problems.[12] The CS also highlights that for patients with later stages of disease, treatment using whole-brain radiotherapy or stereotactic radiosurgery can result in a range of additional complications, including neurocognitive decline, radiation-induced degeneration and hydrocephalus.[16, 17]

Distant metastases in people with resected, early-stage NSCLC is often debilitating and leads to worsening HRQoL impairment as the disease progresses and the patient's performance status (PS) declines. Negative HRQoL impacts may result from relapse or worsening of the disease, high symptom burden as well as adverse effects of treatments. Patients with early-stage NSCLC often experience poor mental health, including symptoms of anxiety and depression. The CS[2] describes further negative impacts of the disease on the HRQoL of caregivers of patients with NSCLC, which can worsen following the onset of progressive disease for the patient, increased symptom burden and functional decline.[18] The CS underscores the importance of keeping patients in a disease-free state and avoiding the negative consequences of distant recurrence with central nervous system (CNS) metastases.

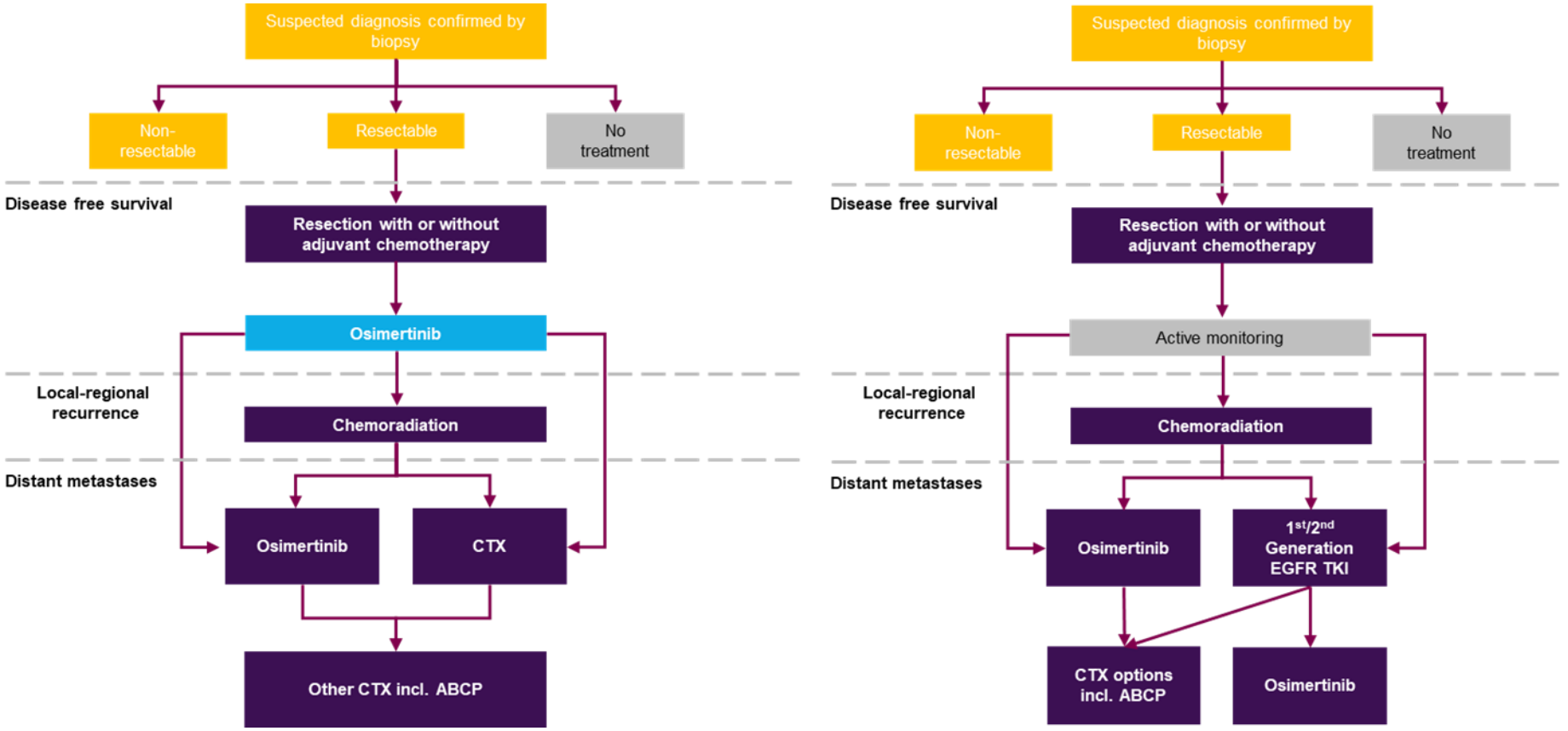
The CS[2] also provides some discussion of the economic burden of the disease, including impacts related to workplace absence and long-term sickness or disability leave, and reports an estimated annual cost to society for resected NSCLC of £267 million (including direct, indirect, and out-of-pocket costs).[19]

2.2 Critique of the company's overview of current service provision

2.2.1 Current treatment pathway for patients with EGFRm NSCLC

The company's view of the current treatment pathway for patients with Stage IB-IIIA EGFRm NSCLC who have undergone complete resection, together with the proposed positioning of osimertinib in routine commissioning, is reproduced in Figure 1. Current recommendations on the use of specific technologies for treating EGFRm NSCLC from the National Institute for Health and Care Excellence (NICE) are summarised in Table 4.

Figure 1: Treatment pathway for resectable EGFRm NSCLC with and without adjuvant osimertinib (reproduced from CS, Figure 3)



Note: The company's anticipated positioning for adjuvant osimertinib is shown in blue
ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel; CTX - chemotherapy; EGFRm - epidermal growth factor receptor mutation; EGFR - epidermal growth factor receptor; TKI - tyrosine kinase inhibitor; NSCLC - non-small cell lung cancer

Table 4: Current NICE recommendations for treatments for EGFRm NSCLC

NICE TA	NICE recommendation
Adjuvant/neoadjuvant treatments	
TA761 - Osimertinib (2022)[20]	Osimertinib is recommended for use within the CDF as adjuvant treatment after complete tumour resection in adults with stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. It is recommended only if it is stopped at 3 years or earlier due to disease recurrence or unacceptable toxicity and if the conditions in the MAA are followed.
Treatments for locally advanced or metastatic disease	
TA654 - Osimertinib (2020)[21]	Osimertinib is recommended, within its marketing authorisation, as an option for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults. It is recommended only if the company provides it according to the commercial arrangement.
TA653 - Osimertinib (2020)[22]	Osimertinib is recommended as an option for treating EGFR T790M mutation-positive locally advanced or metastatic NSCLC in adults, only if their disease has progressed after first-line treatment with an EGFR TKI and the company provides osimertinib according to the commercial arrangement.
TA584 - Atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP) (2019)[23]	ABCP is recommended as an option for metastatic NSCLC in adults who have not had treatment for their metastatic NSCLC before and whose PD-L1 tumour proportion score is between 0% and 49% or when targeted therapy for EGFR-positive or ALK-positive NSCLC has failed. It is recommended only if atezolizumab and bevacizumab are stopped at 2 years of uninterrupted treatment, or earlier if there is loss of clinical benefit (for atezolizumab) or if the disease progresses (for bevacizumab) and the company provide atezolizumab and bevacizumab according to the commercial arrangements.
TA595 - Dacomitinib (2019)[24]	Dacomitinib is recommended, within its marketing authorisation, as an option for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults. It is recommended only if the company provides it according to the commercial arrangement.
TA374 - Erlotinib and gefitinib (2015)[25]	Erlotinib is recommended as an option for treating locally advanced or metastatic NSCLC that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is EGFR-TK mutation-positive, only if the company provides erlotinib with the revised discount agreed in the PAS. Gefitinib is not recommended for treating locally advanced or metastatic NSCLC that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-positive.
TA310 - Afatinib (2014)[26]	Afatinib is recommended as an option, within its marketing authorisation, for treating adults with EGFR-TK positive locally advanced or metastatic NSCLC only if the person has not previously had an EGFR-TK inhibitor and if the conditions in the MAA are followed.
TA258 - Erlotinib (2012)[27]	Erlotinib is recommended as an option for the first-line treatment of people with EGFR-TK positive locally advanced or metastatic NSCLC, only if the conditions in the MAA are followed.
TA192 - Gefitinib (2010)[28]	Gefitinib is recommended as an option for the first-line treatment of people with EGFR-TK positive locally advanced or metastatic NSCLC, only if the conditions in the MAA are followed.

TA - Technology Appraisal; CDF- Cancer Drugs Fund; PAS - Patient Access Scheme; MAA - Managed Access Agreement; PAS - Patient Access Scheme; EGFR - epidermal growth factor receptor; TK - tyrosine kinase; TKI - tyrosine kinase inhibitor; NSCLC - non-small cell-lung cancer; PD-L1 - Programmed death-ligand 1; ALK - anaplastic lymphoma kinase

The company's view of the overall treatment pathway for resectable, early-stage EGFRm NSCLC is summarised briefly below, based on the description provided in Section B.1.3.3 of the CS.[2] Additional comments from the EAG have been integrated into this summary.

Treatment of newly diagnosed EGFRm NSCLC

The staging of NSCLC is conducted according to the American Joint Committee on Cancer (AJCC) staging criteria.[29] The 8th edition of these criteria have been available since 2018. Given the availability of neoadjuvant and adjuvant therapies for early-stage NSCLC, genetic testing for EGFR mutations has become part of standard practice in the NHS in England.

Surgery (complete tumour resection) represents the mainstay of treatment for newly diagnosed EGFRm NSCLC in eligible patients, including those with stage I-II disease or operable stage IIIA disease according to the 7th AJCC Tumour Node Metastasis (TNM) edition. Surgical resection may be complemented by adjuvant cisplatin-based chemotherapy in some patients with early-stage NSCLC and good PS (World Health Organization [WHO] PS 0 or 1). This is consistent with the 2019 NICE guideline on the diagnosis and management of lung cancer (NG122).[30] The CS[2] highlights that adjuvant chemotherapy offers only modest absolute benefits in survival and is associated with substantial toxicity. In November 2021, NICE Technology Appraisal 761 (TA761) recommended the use of osimertinib as adjuvant therapy following complete tumour resection (with or without prior adjuvant chemotherapy) in adults with stage IB to IIIA EGFRm NSCLC within the Cancer Drugs Fund (CDF).[20] Where patients are not considered suitable for adjuvant treatment using osimertinib, active monitoring (routine follow-up and monitoring) may be considered following surgical resection.

Treatments for loco-regional recurrence

According to the CS[2] (Section B.1.3.3), chemoradiation (chemotherapy in combination with radiotherapy) is typically used for the treatment of loco-regional recurrence, although surgery may be an option for a small proportion of patients. Single-modality radiotherapy may also be used in some patients. The EAG notes that the company's treatment pathway diagram (Figure 1) does not include single-modality radiotherapy as an option for patients with loco-regional recurrence. However, the company's economic model does include the use of single-modality radiotherapy for a proportion of patients who develop loco-regional recurrence (see Section 5.2).

Treatments for distant metastases

In the event of locally advanced or distant metastases after complete tumour resection, first-line treatment options in the company's clinical treatment pathway include: (i) osimertinib, (ii) first-generation EGFR tyrosine kinase inhibitors (TKIs) (erlotinib and gefitinib) or second-generation EGFR TKIs (afatinib and dacomitinib), or (iii) platinum-based chemotherapy. Potential treatment options for

patients with distant metastases are dependent on prior adjuvant treatments received, the timing of recurrence, patient fitness, the patient's ability to tolerate treatment-related toxicities, as well as patient choice. The company's view of the treatment pathway includes the use of osimertinib as first-line treatment for patients who have not previously received this therapy in the adjuvant setting, and also as a re-treatment option for some patients who have received adjuvant osimertinib following surgery (with or without adjuvant chemotherapy). This is in line with the marketing authorisation for osimertinib and is consistent with the treatment pathways described in NG122.[30] For those patients who experience disease recurrence during the course of treatment with adjuvant osimertinib, and for those patients who cannot tolerate osimertinib-related toxicity, chemotherapy may be considered as a potential first-line therapy. This is also consistent with NG122. Early generation TKIs may also be used as first-line therapy for some patients with EGFRm NSCLC with distant metastases – these include erlotinib (TA374 and TA258),[25, 27] afatinib (TA310),[26] gefitinib (TA192)[28] and dacomitinib (TA595).[24] However, the use of these earlier TKIs as first-line therapy is generally low at around 17%,[31] as they are considered to be less effective than osimertinib.

For patients who receive osimertinib or an early TKI as first-line treatment for distant metastases, second-line treatment options may include either chemotherapy or atezolizumab plus bevacizumab in combination with carboplatin and paclitaxel (ABCP).[23] The company's pathway includes osimertinib as a second-line treatment option for certain patients whose metastatic disease has progressed after first-line treatment with an early generation TKI. This is consistent with NICE TA653, which recommends osimertinib as a second-line treatment option for patients with EGFR T790 mutation-positive locally advanced or metastatic NSCLC whose disease has progressed after first-line metastatic treatment with an early generation TKI.[22] For those patients who have previously received chemotherapy as first-line treatment for metastatic disease and whose disease has subsequently progressed, the CS^2 states that other chemotherapy options could be given in the second-line setting, although the specific regimens are not clearly described in the company's treatment pathway. The company's economic model assumes that platinum doublet chemotherapy (PDC) is the chemotherapy regimen of choice in the first-line setting, and that docetaxel would be used as second-line therapy if PDC is used as first-line therapy (see Section 5.2).

Section B.1.3.3.3 of the CS^2 also describes the treatment options for brain metastases and bone metastases. Treatment for brain metastases includes symptomatic interventions such as dexamethasone as well as surgery, radiotherapy, or systemic therapies. Single-fraction radiotherapy may be used as palliative treatment for bone metastases.

2.2.2 Company's proposed positioning of osimertinib

The company's proposed positioning of adjuvant osimertinib in England is in line with the full licensed indication for osimertinib,[32] that is, as adjuvant treatment following complete tumour resection in adults with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. This positioning is consistent with how osimertinib has been used as adjuvant treatment within the CDF.

2.2.3 EAG clinical advisors' views

The EAG's clinical advisors broadly agreed with the company's description of the disease and the proposed positioning of adjuvant osimertinib under routine commissioning. One of the EAG's clinical advisors commented that the vast majority of patients who experience distant recurrence go on to receive active first-line therapy with osimertinib for metastatic disease, as most patients remain fit at this stage. However, they stated that following progression on first-line therapy, approximately one-third of patients with metastatic relapse choose palliative treatment/best supportive care (BSC) rather than an active second-line treatment. The EAG's second clinical advisor commented that whilst some patients may discontinue adjuvant osimertinib due to treatment-related toxicity, this would not necessarily preclude re-treatment with osimertinib in the first-line metastatic setting. The EAG's clinical advisors commented that there remains some uncertainty regarding the extent of use of osimertinib in the re-treatment setting, as well as uncertainty around whether its efficacy as re-treatment is the same as that for patients who have not previously received this therapy. One of the EAG's clinical advisors stated that some re-treated patients might develop drug resistance to osimertinib earlier in the metastatic setting, which would likely lead to lower effectiveness.

3. CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[2] A summary of the decision problem as outlined in the final NICE scope[33] and addressed in the CS is reproduced in Table 5. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 5: The decision problem (reproduced from CS, Table 1, with minor amendments by the EAG)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
Population	People with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, after complete tumour resection (with or without adjuvant chemotherapy)	As per scope	N/a
Intervention	Osimertinib	As per scope	N/a
Comparator(s)	• Platinum-based chemotherapy • Established clinical management without osimertinib (that is, active monitoring)	Use of active monitoring as only relevant comparator	As indicated in response to the draft scope, active monitoring is the only appropriate comparator for adjuvant osimertinib. The ADAURA trial was not designed to define the optimal role of adjuvant chemotherapy in resected EGFRm NSCLC patients, and the trial was deliberately designed to evaluate osimertinib as an add-on therapy to standard practice in the adjuvant setting (i.e., surgery plus chemotherapy, if indicated).[34] Adjuvant osimertinib is not intended to displace adjuvant chemotherapy, as it provides an additional option for further adjuvant therapy after the patient/clinician decision to receive/administer adjuvant chemotherapy following complete resection. This is reflected in the marketing authorisation wording,[32] which does not mandate whether or not patients should receive adjuvant chemotherapy prior to initiation of adjuvant osimertinib. Patients in the ADAURA trial, the primary source of evidence for this appraisal, were randomised after the option to receive adjuvant chemotherapy post-resection. DFS, the primary endpoint for the ADAURA trial, was measured from the point of randomisation to the point of disease recurrence or death.[34] Outcomes for patients who received a complete resection but did not progress to eligibility for adjuvant osimertinib treatment e.g., due to early recurrence or deterioration in performance status, have not been captured. Therefore, it would be inappropriate to extend the cost-utility analysis to incorporate costs and consequences prior to the time of randomisation in the trial. It should also be noted that prior chemotherapy use was not a stratification factor in the ADAURA trial and subgroups according to prior adjuvant chemotherapy use were not powered for significance. As such, any analysis of outcomes by prior chemotherapy use are exploratory in nature and not appropriate for incorporation into a cost-utility analysis or for payer decision-making.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
			The Company acknowledges the communication regarding comparator selection provided by NICE on 25th October 2023, which suggests some patients who would previously have chosen to receive adjuvant chemotherapy may now decline adjuvant chemotherapy and instead progress straight to adjuvant osimertinib. As outlined above, adjuvant osimertinib availability is not intended to displace adjuvant chemotherapy use and this is reflected in the ADAURA trial design. In order to conduct the analysis outlined by NICE, a comparison of patients who receive adjuvant chemotherapy and then go on to receive active monitoring versus patients who do not receive adjuvant chemotherapy and then go on to receive adjuvant osimertinib would need to be conducted. For the reasons outlined above (randomisation point, lack of stratification, insufficient powering), there is no available evidence to conduct such an analysis and any attempt to do so, e.g., by using proxy DFS data, would be methodologically unsound and not suitable for payer decision-making. Additionally, the Company is not aware of any evidence to quantify the suggested displacement of adjuvant chemotherapy by adjuvant osimertinib. In summary, active monitoring is the only appropriate comparator for adjuvant osimertinib as it does not displace any other treatment from the current treatment pathway. This is aligned with the original scope (TA761) as there is no clear rationale for deviation.[20]
Outcomes	The outcome measures to be considered include: • Overall survival (OS) • Disease-free survival (DFS) • Sites and rates of recurrence • Time to treatment discontinuation (TTD) • Adverse effects of treatment • Health-related quality of life (HRQoL).	As per scope	N/a
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The economic base case is based on the NICE reference case. A PAS price is applicable for all	N/a

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope
	The reference case stipulates that 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 Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The use of osimertinib is conditional on the presence of an EGFR mutation. The economic modelling should include the costs associated with diagnostic testing for EGFR in people with resectable, early-stage NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual.	osimertinib indications, including the ADAURA indication, in line with the commercial access arrangement formed as part of TA654 and TA653.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • NSCLC stage (IB versus II-IIIA) may be considered.	Whilst pre-specified subgroup data from ADAURA are presented in this submission, the cost-effectiveness analysis is based on the full population.	Pre-specified subgroups were included in the pivotal trial (ADAURA) and the relevant efficacy data are presented in this submission. These subgroups, which were based on demographics, cancer staging, EGFR mutation, and adjuvant chemotherapy, were not powered to detect significant effects. 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.
Special considerations including issues related to equity or equality	N/a	N/a	N/a

CS - company's submission; EAG - External Assessment Group; NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; NSCLC - non-small cell lung cancer; EGFR - epidermal growth factor receptor; PAS - Patient Access Scheme; N/a - not applicable

3.1 Population

The target population for adjuvant osimertinib defined in the CS[2] relates to adult patients who have undergone complete tumour resection, with or without adjuvant chemotherapy, and who have stage IB-IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. This target population is consistent with both the final NICE scope[33] and the full Medicines and Healthcare products Regulatory Agency (MHRA)/European Medicines Agency (EMA) marketing authorisation for osimertinib.[32, 35]

The clinical data presented in the CS[2] are based on the ADAURA trial of adjuvant osimertinib versus placebo.[36] The CS (Section B.2.2) states that ADAURA included adults with a WHO PS 0-1, primary non-squamous NSCLC following complete resection, with post-surgical pathological stage IB−IIIA and centrally-confirmed EGFR exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations, treated with or without prior adjuvant chemotherapy. The EAG's clinical advisors commented that the ADAURA trial population is broadly consistent with the population of patients who would be considered for treatment with adjuvant osimertinib in NHS clinical practice. Summary data from the Systemic Anti-Cancer Therapy (SACT) database provided in CS Appendix R[37] suggest that NHS patients who have received adjuvant osimertinib are slightly less fit than the ADAURA trial population, with fewer patients with a PS of 0 in SACT. Fewer patients in SACT received prior adjuvant chemotherapy than in ADAURA (proportion with prior chemotherapy: SACT = 27%; ADAURA = 60%).

3.2 Intervention

The intervention included in the CS[2] is osimertinib (Tagrisso®) given as an adjuvant treatment. This is consistent with the final NICE scope.[33] Osimertinib is an oral, CNS-active TKI that targets EGFR exon 19 deletions or exon 21 (L858R) substitution mutations of the EGFR-TK. Osimertinib has a current MHRA/EMA marketing authorisation for three NSCLC indications: (i) for the adjuvant treatment of adults with stage IB-IIIA EGFRm NSCLC (the indication which is most relevant to this appraisal); (ii) as first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations, and (iii) as treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.[32] Within the adjuvant therapy indication, the Summary of Product Characteristics (SmPC) states that osimertinib as monotherapy is indicated for: *"the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations."* Both the CS and the SmPC state that EGFR mutation status should be confirmed in tumour or plasma specimens using a validated method of testing.

The recommended daily dose of osimertinib is 80mg.[32] The list price for 30 x 80mg tablets is £5,770.[38] A Patient Access Scheme (PAS) discount of [redacted] is available for osimertinib in the adjuvant indication. The cost per pack of osimertinib including this discount is [redacted].

The definition of the intervention detailed in the NICE scope[33] does not specify a maximum treatment duration for adjuvant osimertinib. The SmPC for osimertinib[32] (page 5) states: *"Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied."* This implies (but does not stipulate) that adjuvant treatment with osimertinib should be discontinued after 3 years of treatment. One of the EAG's clinical advisors stated that they would not want to offer adjuvant osimertinib to patients for more than 3 years due to the burden of taking continued therapy, whilst the second clinical advisor commented that since its entry into the CDF, clinicians have been unable to offer adjuvant treatment with osimertinib beyond 3 years due to the Blueteq criteria. Within the ADAURA trial,[36] patients randomised to the intervention group received osimertinib 80mg once daily for 3 years or until disease recurrence or fulfilment of a criterion for treatment discontinuation. The company's health economic model includes a stopping rule whereby the maximum treatment duration for adjuvant osimertinib is assumed to be 3 years.

The SmPC[32] lists the following special warnings and precautions for the use of osimertinib across the adjuvant and metastatic settings:

- Interstitial Lung Disease (ILD): Severe, life-threatening or fatal ILD or ILD-like adverse reactions (e.g., pneumonitis) have been observed in patients treated with osimertinib in clinical studies. Most cases improved or resolved with interruption of treatment. Patients with a past medical history of ILD were excluded from clinical studies. ILD or ILD-like adverse reactions were reported in 3.8% and were fatal in 0.3% (n=5) of the 1,479 patients who received osimertinib in ADAURA, FLAURA and AURA studies (no fatal cases were reported in the adjuvant setting, i.e., the ADAURA trial). The incidence of ILD was 11.3% in patients of Japanese ethnicity, 1.6% in patients of Asian ethnicity and 2.5% in non-Asian patients.
- Severe cutaneous adverse reactions (SCARs): Case reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported rarely in association with osimertinib treatment.
- Corrected QT (QTc) interval prolongation: Occurs in patients treated with osimertinib. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias or sudden death. No arrhythmic events were reported in the ADAURA, FLAURA or AURA studies.
- Changes in cardiac contractility: Across clinical trials, left ventricular ejection fraction (LVEF) decreases greater than or equal to 10 percentage points and a drop to less than 50% occurred in 3.2% (40/1233) of patients treated with osimertinib who had baseline and at least one follow-up LVEF assessment. In ADAURA, 1.6% (5/312) of patients treated with osimertinib and 1.5%

(5/331) of patients treated with placebo experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

- Keratitis: Keratitis was reported in 0.7% (n=10) of the 1,479 patients treated with osimertinib in the ADAURA, FLAURA and AURA studies.
- Aplastic anaemia: Aplastic anaemia, including fatal events, have been reported rarely in association with osimertinib treatment.
- Age and body weight: Elderly patients (>65 years) or those with low body weight (<50 kg) may be at increased risk of developing adverse events (AEs) of Grade 3 or higher.

3.3 Comparators

The CS[2] includes a single comparator - established clinical management without osimertinib (active monitoring i.e., routine imaging and follow-up). This is consistent with one of the two comparators listed in the final NICE scope[33] and reflects the control group in the ADAURA trial,[36] whereby patients received placebo for 3 years or until disease recurrence or fulfilment of a criterion for treatment discontinuation.

The final NICE scope[33] also lists (adjuvant) platinum-based chemotherapy as a second comparator. As summarised in Table 5, the CS[2] presents several arguments regarding why adjuvant chemotherapy should not be considered as a relevant comparator for osimertinib:

- Adjuvant osimertinib is not intended to displace chemotherapy as it provides as additional option for further adjuvant therapy after the patient/clinician decision to receive/administer adjuvant chemotherapy.
- Patients who were enrolled in the ADAURA trial[36] were randomised after the option to receive adjuvant chemotherapy following complete resection; hence, outcomes were measured from randomisation, not from the initiation of first adjuvant therapy. Comparing outcomes for therapies given at different points in the treatment pathway would inappropriately introduce a selection bias.
- Prior chemotherapy use was not a stratification factor in the ADAURA trial[36] and subgroups defined by receipt of adjuvant chemotherapy were not adequately powered.
- There is no available evidence that would permit a robust comparison between adjuvant osimertinib and adjuvant chemotherapy.
- The original appraisal of adjuvant osimertinib for EGFR mutation-positive NSCLC – NICE TA761[20] – did not include adjuvant chemotherapy as a comparator and there is no clear rationale for deviating from the scope of this earlier appraisal.

The EAG's clinical advisors did not consider adjuvant chemotherapy to be a relevant comparator for adjuvant osimertinib. The EAG notes that the use of prior chemotherapy in the SACT population

appears to be substantially lower than that in ADAURA trial (60% versus 27%) which might imply that patients are bypassing chemotherapy and receiving osimertinib directly after undergoing surgical resection. However, the EAG's clinical advisors also commented that the comparatively lower use of chemotherapy in NHS practice may be due to osimertinib providing an additional treatment option for patients who would otherwise not be able to receive any active adjuvant therapy. Overall, the EAG agrees that adjuvant chemotherapy is not a relevant comparator for adjuvant osimertinib. This issue is discussed further in Section 5.3.6.

3.4 Outcomes

The following outcomes are listed in the final NICE scope:[33]

- Overall survival (OS)
- Disease-free survival (DFS)
- Sites and rates of recurrence
- Time to treatment discontinuation (TTD)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS[2] reports on all of these outcomes for the ADAURA trial.[36] All outcomes except for TTD are reported in the clinical effectiveness section of the CS. The company's economic model includes data from ADAURA on DFS, site of recurrence, TTD, AEs and HRQoL. Mortality risks for specific model health states are informed by external data,[39-41] but have been re-calibrated to better align the model predictions with the OS observed in ADAURA. Further details of the company's economic analyses are presented in Chapter 5.

3.5 Subgroups

The final NICE scope[33] states that if evidence allows, subgroup analyses by disease stage (IB versus IIIA) will be considered. Efficacy data for pre-specified subgroups for the ADAURA trial,[36] based on demographics, smoking history, cancer stage, EGFR mutation, and adjuvant chemotherapy are presented in Section B.2.6.1 of the CS.[2] The CS states that there are no subgroups within the population that should be considered separately, as the subgroup analyses in ADAURA demonstrate that the relative treatment effect on OS was consistent across subgroups. The CS also states that patients with Stage IB disease comprise only 212 patients with 63 events across both arms which is insufficient for robust decision-making. The EAG agrees that the available data for the Stage IB subgroup in ADAURA are limited, but notes that the absence of economic subgroup analyses means that heterogeneity cannot be explored. The EAG's clinical advisors commented that they would want to be able to offer adjuvant osimertinib to all eligible patients, regardless of disease stage.

3.6 Other relevant factors

The CS[2] (Section B.1.4) states that no equality considerations have been identified in terms of patient access to osimertinib in UK clinical practice.

The company's economic analyses do not include additional QALY weighting to account for disease severity. The EAG believes that the relevant severity weight for adjuvant osimertinib is 1.0. Further details are provided in Section 5.2.6.

4. CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness and safety evidence for the use of adjuvant osimertinib for the treatment of adults with stage IB-IIIA EGFRm NSCLC after complete tumour resection (with or without prior chemotherapy). The CS[2] reports a systematic literature review (SLR) capturing evidence from the ADAURA trial, and also presents supporting data from SACT relating to the use of adjuvant osimertinib in clinical practice in England during the period of managed access through the CDF. Section 4.1 provides a summary and critique of the company's SLR methods. Section 4.2 summarises the methods and results of the ADAURA trial and describes the available data from SACT. Section 4.3 presents a discussion of the available clinical effectiveness and safety evidence for osimertinib.

4.1 Critique of the methods of review

The CS[2] (Section B.2.1) and CS Appendix D[37] (Section D.1) state that an SLR was conducted to identify publications reporting on the clinical efficacy and safety of adjuvant therapies for the treatment of stage IB–IIIA NSCLC. The supporting documents provided by the company (the main CS[2] and CS Appendix D[37]) state that the search strategies used in the SLR were broad and were designed with the intention of informing a number of workstreams relating to osimertinib. Only studies of adjuvant treatment in the EGFRm NSCLC population and studies relating to the use of adjuvant osimertinib in this population were included in CS Appendix D[37] and the main CS,[2] respectively.

4.1.1 Searches

CS Appendix D.1[37] reports the literature searches conducted to identify published and unpublished evidence of clinical effectiveness and safety in relation to the decision problem. As the searches were intended to be used for multiple purposes, they addressed a broader population which included, but which was not restricted to, patients with EGFRm NSCLC.

The company conducted searches in July 2020 and updated these in October 2023. These searches covered all of the core databases required by NICE (MEDLINE-ALL, Embase, CENTRAL), plus a selection of relevant conference proceedings and the WHO International Clinical Trial Registry Platform (ICTRP). The search strategies themselves, which are reported in full in CS Appendix D.1.1.1,[37] are well-designed, and included an appropriate range of subject headings and free text terms for the population and interventions of interest. Whilst there are areas for potential improvement (e.g., the addition of a truncation character (*) after "receptor" in line 13, which would have retrieved the plural as well as the singular form of this term), these are only minor errors, the impact of which is likely to be minimal.

Study filters were based on those devised by the Scottish Intercollegiate Guidelines Network (SIGN), albeit with modifications. In their response to clarification questions from the EAG (question A2),[42] the

company provided full details of the changes they made to these filters. However, the EAG advises that the credibility associated with using validated expert search strategies depends to a large extent on them being used in their original, tried-and-tested form.

Despite these minor concerns, the EAG regards the company's searches as having been executed competently, meaning that the risk of missing any relevant studies is low.

4.1.2 Inclusion criteria for the SLR

CS Appendix D[37] (Table 15, page 35) presents the eligibility criteria for the SLR restricted to the EGFRm population only. Inclusion criteria were as follows:

- Population: Patients with EGFRm stage IB–IIIA NSCLC following complete tumour resection
- Intervention: Any treatment for stage IB–IIIA NSCLC following complete tumour resection
- Comparators: Any or no comparators
- Outcomes: Includes all those listed in the decision problem (see Table 5)
- Study design: Randomised controlled trials (RCTs), non-RCTs, observational studies, systematic reviews and meta-analyses
- Publication type: Peer-reviewed journal articles; conference abstracts published in or after 2018
- Other considerations: Only studies in humans; English language publications only.

CS Appendix D[37] states that two reviewers independently examined abstracts and full-text articles to select relevant studies. Disagreements were resolved by discussion until a consensus was achieved. The EAG considers this to reflect good practice.

Of the studies identified using the above-mentioned pre-defined eligibility criteria, only one study evaluating adjuvant osimertinib – the ADAURA RCT[36] – was considered eligible for inclusion within the CS.[2] The EAG considers the inclusion of ADAURA to be appropriate and in line with the final NICE scope.[33]

4.1.3 Inclusion criteria for the indirect comparison

No indirect comparison was undertaken.

4.1.4 Critique of data extraction

CS Appendix D[37] (page 37) states that data were extracted into a Microsoft Excel form by one reviewer and independently checked by a second reviewer. Any missing information or discrepancies were discussed and resolved by consensus. The EAG considers this to reflect good practice.

4.1.5 Quality assessment

The quality of RCTs (including ADAURA[36]) was assessed using the York Centre for Reviews and Dissemination (CRD) checklist for RCTs.[43] One reviewer initially conducted the quality assessment and a second reviewer subsequently verified the decisions. Differences were resolved by discussion and consensus. The EAG considers these methods to be appropriate.

4.1.6 Evidence synthesis

Section B.2.8 of the CS[2] reports that the ADAURA RCT[36] was the only relevant clinical trial identified; therefore, a meta-analysis was not performed.

Section B.2.9 of the CS[2] states that an indirect treatment comparison (ITC) was not necessary because ADAURA compared adjuvant osimertinib to the relevant comparator (placebo plus active monitoring). In their clarification response[42] (question B1), the company explained that no available data exist with which to perform an ITC between adjuvant osimertinib (with or without prior adjuvant chemotherapy) versus adjuvant chemotherapy alone. The company also stated that choices about adjuvant treatment with osimertinib and chemotherapy in the relevant population relate to "*two separate and sequential decisions.*"[42] As discussed in Section 3.3, the EAG agrees that adjuvant chemotherapy is not a relevant comparator for adjuvant osimertinib and that it is unclear how a reliable ITC could have been conducted.

4.1.7 Ongoing studies

The CS[2] (Section B.2.11) states that there are no ongoing studies of osimertinib which are relevant to the current appraisal. The EAG identified two ongoing studies of adjuvant osimertinib, both of which are sponsored by AstraZeneca (see Table 6). ADAURA is the main study under consideration in this appraisal and is listed as "Active, not recruiting" on clinicaltrials.gov. TARGET is an ongoing open-label Phase 2 study assessing the efficacy and safety of osimertinib in EGFRm stage II-IIIB NSCLC, following complete tumour resection. This latter study could provide additional data on DFS, OS, recurrence rates and safety for the stage II-IIIA subgroup. However, this study was only initiated in 2023 and study completion is not expected until 2029.

[redacted]

Table 6: Ongoing studies of adjuvant osimertinib

Study name	Design	Population	Intervention	Comparator(s)	Key outcomes	Study start date	Study completion date*	Date of last update of trial record
ADAURA2[44, 45] NCT05120349	Phase III, 2-arm randomised controlled study	EGFRm-positive stage IA2-IA3 NSCLC, following complete tumour resection	Osimertinib	Placebo	**DFS in high-risk subgroup** DFS CNS DFS OS HRQoL	Feb 2022	Nov 2032	Jan 2024
TARGET[46, 47] NCT05526755	Phase II open-label, single arm study	EGFRm-positive stage II-IIIB NSCLC, following complete tumour resection	Osimertinib with or without chemotherapy	N/a	**DFS** DFS rate at 3, 4 and 5 years OS Recurrence rate AEs	March 2023	April 2029	Feb 2024

Bold text *indicates the primary outcome of study*
**Estimated dates*
CNS - central nervous system; DFS - disease-free survival; EGFRm - epidermal growth factor receptor mutation; N/a - not applicable; NSCLC - non-small cell lung cancer; OS - overall survival; AE - adverse event

4.2 Summary and critique of the included studies

The company's SLR identified a single randomised RCT - the ADAURA trial (NCT02511106).[36] The EAG notes that the long-term benefits of adjuvant osimertinib on DFS and OS were highlighted as key areas of uncertainty in NICE TA761.[20] Section B.2 of the CS[2] states that the results presented in the current submission relate to the updated analyses of ADAURA, reflecting data cut-offs (DCOs) of the 11th April 2022 for DFS and the 27th January 2023 for OS. The company's clarification response[42] (question B2) explains that the planned analyses of DFS and OS were not linked but were instead event-driven. DFS outcomes reached the pre-specified level of maturity (approximately 50% in the stage II-IIIA population) at the April 2022 DCO. The company's clarification response also states that the DCO for DFS was recommended by the Independent Data Monitoring Committee (IDMC) at the time of early unblinding at trial level (in April 2020) when the interim analysis of ADAURA was undertaken. The company explains that the final analysis of OS was planned when data maturity reached approximately 20% (i.e., 94 events observed) and notes that OS data maturity was 18% at the January 2023 DCO.

4.2.1 Study design: ADAURA

ADAURA (NCT02511106)[36, 48, 49] is a multicentre, Phase 3, randomised, double-blinded, placebo-controlled study. ADAURA examined the efficacy and safety of adjuvant osimertinib. ADAURA was conducted in 212 centres in 24 countries across Europe, Asia-Pacific, North America, and South America. Based on the clinical study report (CSR) for ADAURA, none of the sites were in the UK. Eligible patients were adults with completely resected stage IB to IIIA (based on the AJCC/Union for International Cancer Control (UICC) staging system, 7th edition), EGFRm-positive (Ex19del or L858R) primary non-squamous NSCLC; treated with or without adjuvant chemotherapy; and with a WHO PS of 0 or 1. The EAG's clinical advisors stated that the inclusion criteria for the trial were appropriate.

Patients were stratified according to disease stage (IB, II, or IIIA), EGFR mutation status (Ex19del or L858R), and race (Asian or non-Asian). Six hundred and eighty-two patients were assigned in a 1:1 ratio to receive either osimertinib (80mg once daily, N=339) or placebo (i.e., established clinical management following tumour resection, N=343) for 3 years. Treatment continued until completion of the treatment duration, disease recurrence or until a treatment discontinuation criterion was met.[48, 49]

The study characteristics and exclusion criteria of the ADAURA trial[48, 49] are summarised in Table 7 and Table 8, respectively.

Table 7: ADAURA, study characteristics (adapted from CS, Tables 5, 6, and 7, and Figure 4)

Trial Name	Study design	Countries	Population	Intervention (N)	Comparator (N)	Treatment duration and follow-up	Stratification factors	Analysis populations	Subgroup analyses (DFS and OS)
ADAURA Wu *et al.*, 2020[34] Herbst *et al*., 2023[48] Tsuboi *et al*., 2023[49] CSR[36]	RCT (Phase 3, double-blind, multi-centre trial)	24 countries across Europe, Asia-Pacific, North America, and South America (N=212 sites)	Adults aged ≥18 (or aged≥20 in Japan and Taiwan). Primary non-squamous completely resected NSCLC with post-surgical pathological stage IB−IIIA Centrally-confirmed EGFR Ex19del or L858R mutation Treated with or without adjuvant chemotherapy WHO PS 0–1	Osimertinib 80 mg once daily (N=339) Reduced to 40mg/day if clinically significant AEs or unacceptable toxicity	Placebo (established clinical management following tumour resection) (N=343)	*Duration*: 3 years or until disease recurrence or meeting a treatment discontinuation criterion. Unblinded two years early due to overwhelming efficacy with osimertinib. *Follow-up*: Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly. After recurrence: Every 24 weeks for 5 years, then yearly.	Stage (IB vs. II vs. IIIA) EGFRm type (Ex19del vs. L858R) Race (Asian vs. non-Asian)	Overall population all patients: stage IB-IIIA (focus of CS[2]) Primary study population: stage II-IIIA	Gender Age Smoking history Race Stage EGFR mutation Adjuvant chemotherapy

CS - company submission; DFS - disease-free survival; EGFR - epidermal growth factor receptor; Ex19del - exon 19 deletion; NSCLC - non-small cell lung cancer; PS - performance status; WHO - World Health Organization

Table 8: ADAURA, exclusion criteria (adapted from CS, Table 7)

Exclusion criteria
• Any disallowed treatment (pre/postoperative/planned radiation therapy for current lung cancer; neo-adjuvant chemotherapy; prior anticancer therapy for NSCLC other than platinum-based doublet postoperative adjuvant chemotherapy; prior treatment EGFR-TKI; major surgery within 4 weeks of the first dose; medications or herbal supplements known to be potent inducers of CYP3A4 (at least 3 weeks prior); treatment with other investigational drug) • Segmentectomies or wedge resections • Unresolved toxicities from prior therapy greater than CTCAE Grade 1 (exceptions included alopecia and Grade 2 prior platinum-therapy-related neuropathy) • Evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, or active infection including hepatitis B, hepatitis C and HIV • Any of the following cardiac criteria: mean resting QTc >470 msec; clinically important rhythm, conduction, or ECG morphology abnormalities; factors that increase the risk of QTc prolongation or risk of arrhythmic events • Active or historical ILD • Inadequate bone marrow reserve or organ function.

CTCAE - Common Terminology Criteria for Adverse Events; EGFR - epidermal growth factor receptor; TKI - tyrosine kinase inhibitor; ILD - interstitial lung disease; NSCLC - non-small cell lung cancer; ECG - electrocardiogram; HIV - human immunodeficiency virus

The CS[2] reports results for the following outcomes in the ADAURA trial:[36]

- DFS
- OS
- Sites, rates, types and timing of recurrence
- CNS recurrence (a *post hoc* endpoint)
- TTD (reported in the cost-effectiveness section of the CS)
- HRQoL
- AEs.

4.2.2 Planned analyses in ADAURA

Statistical analyses and definitions of study groups for the clinical effectiveness analyses in ADAURA[36] are summarised in Table 9. Analysis populations included the full analysis set (FAS) and the safety analysis set (SAS). The FAS, which is also referred to as the 'overall population', included all randomised patients (stage IB-IIIA patients, N=682). This is the population of most relevance to the current appraisal, as it reflects the full marketing authorisation for the adjuvant therapy indication of osimertinib. The CS[2] (Section B.2.4) states that the CSR-defined primary study population was a subset of the FAS,[36] which comprised all patients with stage II-IIIA disease (N=470). An intention-to-treat (ITT) analysis was used to compare treatment groups in the FAS. The SAS consisted of all patients receiving at least one dose of study treatment. The EAG notes that the CS[2] presents clinical effectiveness

results for the most recent DCOs of ADAURA with 95% confidence intervals (CIs); this differs from the earlier interim analyses which presented findings with 99.12% or 99.06% CIs.

Table 9: ADAURA, analysis groups (adapted from CS, Figure 6, and Section B.2.4)

Analysis population	Description	Osimertinib N	Placebo N	Total N
Primary study population	All randomised patients with stage II-IIIA disease	233	237	470
Overall population (FAS)	All randomised patients (stage IB-IIIA) Intention-to-treat basis *Main focus of CS*	339	343	682
SAS	All patients receiving at least 1 dose of study treatment	337	343	680

N - number; CS - company submission; FAS - full analysis set; SAS - safety analysis set

4.2.3 Patient flow and treatment duration in ADAURA

Patient flow in ADAURA[48] at the time of the final DFS analysis (DCO April 2022) is summarised in Table 10. All patients in ADAURA had completed or stopped study treatment at the time of the final DFS analysis. Of the 682 patients randomised, two patients in the osimertinib group did not receive their allocated treatment.

The median duration of treatment exposure in the osimertinib and placebo arms was 35.8 months and 25.1 months, respectively.[49] Overall, [redacted] of patients in the osimertinib arm (N=222/339) and [redacted] of patients in the placebo arm (N=139/343) completed the planned treatment duration of 3 years. In the osimertinib group, early treatment discontinuation was most frequently due to an AE (12.2%), patient decision (10.1%), or disease recurrence (9.8%). In the placebo arm, discontinuations were most commonly due to disease recurrence (50.1%), patient decision (3.5%), or AEs (3.2%). At the final OS DCO of January 2023, the median follow-up for OS in the overall stage IB-IIIA population was 60.4 months in the osimertinib arm and 59.4 months in the placebo arm. The CS[2] (Section B.2.4.2) notes that ADAURA was not powered for OS.

Table 10: ADAURA, patient flow (adapted from CS, Figure 5, and Section B.2.3.2)

Description	Osimertinib N	Placebo N	Total N
All randomised patients (stage IB-IIIA)	339	343	682
Did not receive treatment	2	0	2
Completed 3 years of treatment	222	139	361
Discontinued treatment: Adverse event Patient decision Disease recurrence Other Protocol non-compliance	114* 41 34 33 6 0	204 11 12 172 6 3	318
Patients in study at data cut-off: Completed*** Patient withdrawal Lost to follow-up Death Other	3 261 24 6 42 3	2 234 21 4 82 0	5**
Median duration of treatment exposure	35.8 months	25.1 months	NR
Median follow-up for OS (DCO of 27 January 2023)	60.4 months	59.4 months	NR

**One patient in the osimertinib group discontinued the intervention due to patient decision in 2019 but was documented as continuing osimertinib treatment at DCO 27 January 2023, due to partial data imputation.*
*** No patients received ongoing study treatment after 3 years. Three patients in the osimertinib group and two patients in the placebo group were shown as ongoing treatment at DCO 27 January 2023 due to a data entry error.*
**** Patients who completed the study were in disease-free or overall survival follow-up when the study ended.*
DCO - data cut-off; N - number; NR - not reported; OS - overall survival

4.2.4 Quality assessment of ADAURA

The quality assessment presented in the CS[2] (Section B.2.5) indicates that ADAURA[48, 49] is a well-conducted trial with appropriate randomisation, concealment of treatment allocation, well-balanced baseline characteristics between arms, appropriate blinding of care providers, participants and investigators, and no unexpected imbalances in drop-outs between arms. In addition, all relevant outcomes were reported, and outcomes were analysed as ITT. The EAG agrees with the company's quality assessment and considers ADAURA to be at low risk of bias.

4.2.5 Baseline characteristics: ADAURA

Baseline patient characteristics in ADAURA[34, 36] are summarised in Table 11. In terms of generalisability to the UK population, the EAG's clinical advisors stated that the median age of patients in ADAURA was relatively young for an NSCLC population but may be generalisable to an EGFRm-positive NSCLC population. The EAG's clinical advisors also noted that patients in ADAURA had fewer comorbidities than those seen in NHS clinical practice in England.

Table 11: ADAURA, key patient demographics and baseline characteristics (reproduced from CS, Tables 8 and 9)

Characteristic (FAS)	Osimertinib N=339	Placebo N=343
Median age, years (range)	64 (30–86)	62 (31–82)
Male gender, %	109 (32)	95 (28)
Race, n (%)		
White	122 (36)	122 (36)
Asian	216 (64)	218 (64)
Other	1 (<1)	2 (1)
Missing	0	1 (<1)
Smoking status, n (%)		
Never	231 (68)	257 (75)
Former	104 (31)	83 (24)
Current	4 (1)	3 (1)
Median body mass index, kg/m^2 (range)	[redacted]	[redacted]
WHO performance status, n (%)		
0	216 (64)	218 (64)
1	123 (36)	125 (36)
AJCC stage at diagnosis, n (%)		
IB	107 (32)	109 (32)
II	115 (34)	116 (34)
IIIA	117 (35)	118 (34)
EGFR mutations, n (%)		
Exon 19 deletions	185 (55)	188 (55)
L858R	153 (45)	155 (45)
Histology type, n (%)		
Adenocarcinoma		
Acinar	85 (25)	82 (24)
Papillary, malignant	43 (13)	44 (13)
Malignant	183 (54)	188 (55)
Bronchiolo-alveolar	11 (3)	13 (4)
Solid with mucous formation	4 (1)	5 (1)
Bronchial gland carcinoma (NOS)	1 (<1)	2 (1)
Carcinoma, adenosquamous, malignant	4 (1)	5 (1)
Other	8 (3)	4 (1)
Lung cancer resection type, n (%)		
Lobectomy	328 (97)	322 (94)
Sleeve resection	1 (<1)	3 (1)
Bilobectomy	7 (2)	8 (2)
Pneumonectomy	3 (1)	10 (3)
Regional lymph nodes, %		
N0	138 (41)	144 (42)
N1	97 (29)	97 (28)
N2	104 (31)	102 (30)
Adjuvant chemotherapy, n (%)		
Stage IB, received chemotherapy	27 (25)	30 (28)
Stage II, received chemotherapy	80 (70)	85 (73)
Stage IIIA, received chemotherapy	95 (81)	92 (78)

AJCC - American Joint Committee on Cancer; EGFR - epidermal growth factor receptor; FAS - full analysis set; NOS - not otherwise specified; WHO - World Health Organization

4.2.6 Clinical effectiveness results: ADAURA

Clinical effectiveness results for ADAURA[48, 49] are presented in CS Section B.2.6.[2] The results of the first interim analysis (DCO January 2020) were presented within the company's earlier submission for NICE TA761.[20] The current CS is based on updated analyses of ADAURA, with DCOs of the 11th April 2022 for DFS and the 27th January 2023 for OS.

The CS[2] states that the main population of relevance to the submission is the "overall ADAURA population", i.e., all randomised stage IB-IIIA patients. However, the primary endpoint for ADAURA[36] was DFS by investigator assessment reported in patients with stage II-IIIA disease.[48] The EAG confirms that the effectiveness results based on the updated analyses in the CS[2] appear consistent with those reported in the primary study publications (Herbst *et al.*[48] and Tsuboi *et al.*[49]*)* and the ADAURA CSR.[36]

4.2.6.1 Primary efficacy outcome - Disease-free survival

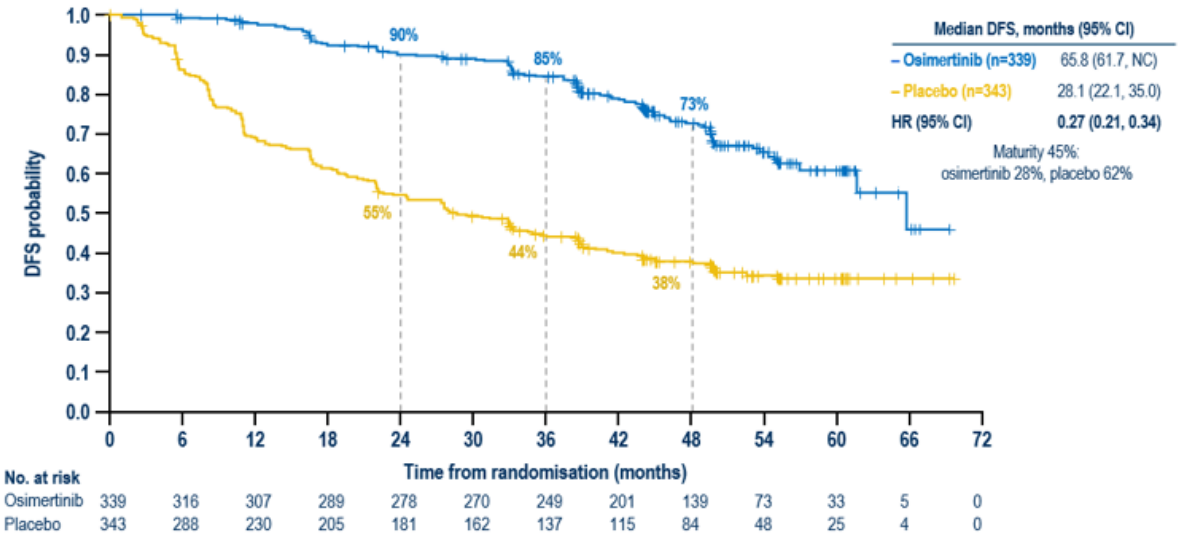
The primary efficacy outcome in ADAURA was DFS.[48] The CS[2] reports a median follow-up duration of 44.2 months (range 0 to 69 months) in the osimertinib group and 27.7 months (range 0 to 70 months) in the placebo group. Planned maturity for the DFS analysis was 50% in the stage II-IIIA population. The CS[2] (Section B.2.6.1.1) notes an increase in DFS data maturity for the overall population from 29% to 45% between the time of the interim analysis (DCO January 2020) and the final analysis (DCO April 2022). For the same period, there was an increase in the maturity of DFS data from 33% to 51% in the stage II-IIIA subgroup. The CS states that the results of ADAURA suggest a consistent and sustained DFS benefit in favour of osimertinib versus placebo between the primary and final analyses for both the overall and stage II-IIIA populations. Table 12 summarises the DFS outcomes for the interim and final analyses. Kaplan-Meier plots of DFS in the overall population, the stage II-IIIA subgroup and the stage IB subgroup, based on the April 2022 DCO, are presented in Figure 2, Figure 3, and Figure 4, respectively.

Table 12: ADAURA, DFS results at the interim and final analysis (adapted from CS, Section B.2.6.1 and Table 12)

Analysis (DCO)	Population	Data maturity	Outcome	Treatment groups		Risk of disease recurrence or death (HR, CI)
				Osimertinib	Placebo	
Interim analysis (Jan 2020)[34]	Overall population	29%	Median DFS (months)	Not reached	27.5	HR 0.20; 99.12% CI 0.14, 0.30; *p*<0.001
			Disease-free at 48 months (%)	N/a	N/a	
	Stage II-IIIA subgroup	33%	Median DFS (months)	Not reached	19.6	HR 0.17; 99.06% CI 0.11, 0.26; *p*<0.001
			Disease-free at 48 months (%)	N/a	N/a	
Final analysis (April 2022)[48]	Overall population	45%	Median DFS (months)	65.8	28.1	HR 0.27; 95% CI 0.21, 0.34; *p*=NR
			Disease-free at 48 months (%)	[redacted]	[redacted]	
	Stage II-IIIA subgroup	51%	Median DFS (months)	65.8	21.9	HR 0.23; 95% CI 0.18, 0.30; *p*=NR
			Disease-free at 48 months (%)	[redacted]	[redacted]	

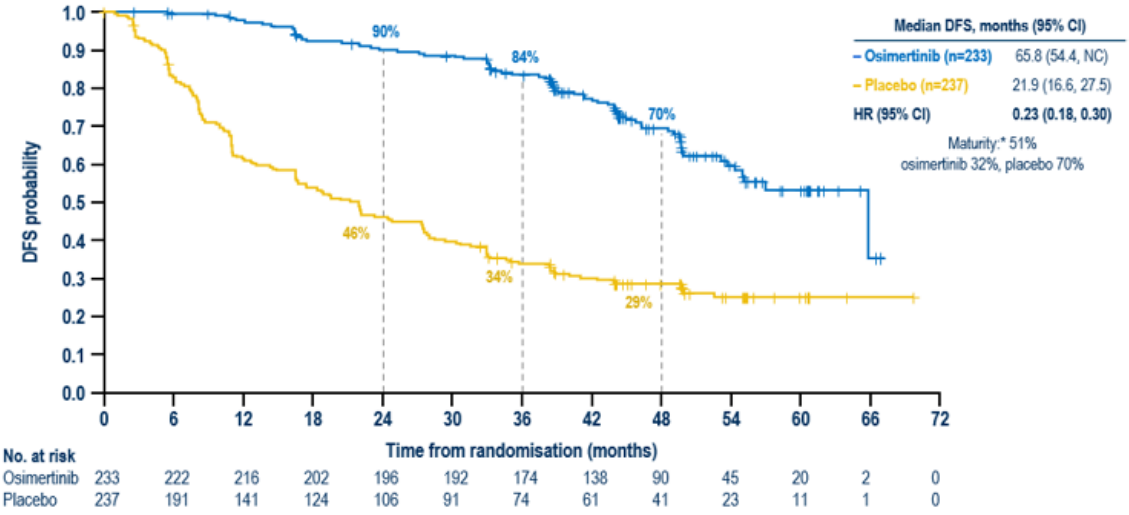
DCO April 2022 (final analysis), 682 patients were included in the overall population (osimertinib, n=339; placebo, n=343).
DCO April 2022 (final analysis), 470 patients were included in the stage II-IIIA subgroup (osimertinib, n=233; placebo, n=237)
DCO - data cut-off; HR - hazard ratio; CI - confidence interval; N/a - not applicable; NR - not reported

Figure 2: Kaplan-Meier plot of DFS in ADAURA, overall population (reproduced from CS, Figure 6)



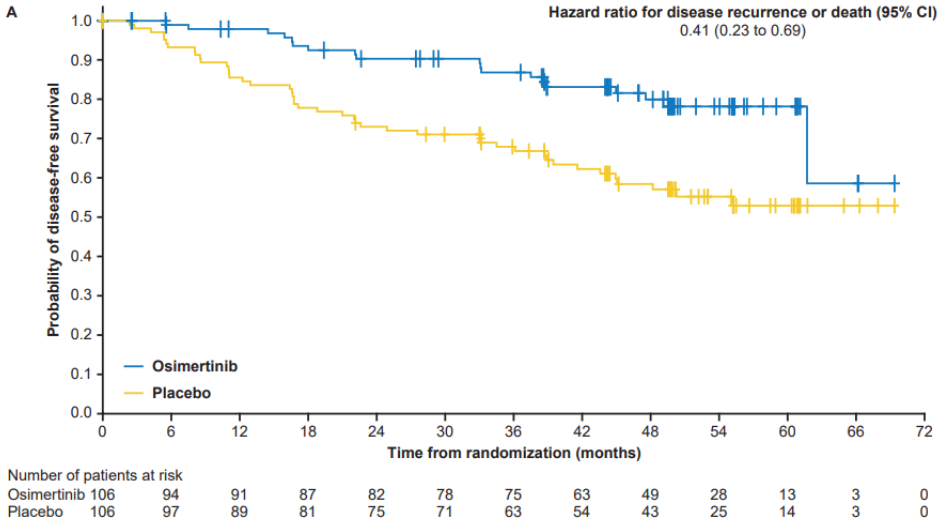
DFS - disease-free survival; HR - hazard ratio; CI - confidence interval; NC - not calculated

Figure 3: Kaplan-Meier plot of DFS in ADAURA, stage II-IIIA subgroup (reproduced from CS, Figure 7)



DFS - disease-free survival; HR - hazard ratio; CI - confidence interval; NC - not calculated

Figure 4: Kaplan-Meier plot of DFS in ADAURA, stage IB subgroup (reproduced from clarification response, question B4)



CI - confidence interval

DFS rate

Data from the final DFS analysis (DCO April 2022) in the overall population and the stage IB and stage II-IIIA subgroups demonstrated a sustained DFS benefit for osimertinib at 36, 48, and 60 months (see Table 13).[2, 48] In the overall population, at 48 months, [redacted] of patients in the osimertinib group were alive and disease-free compared with [redacted] in the placebo group, representing a near-double increase in the DFS rate for patients treated with osimertinib.[48] The CS[2] (Section B.2.6.1.1) states that the Kaplan-Meier DFS function in the placebo group is starting to plateau at around 48 months, but that the interpretation of the DFS function for the osimertinib group is limited by the high level of censoring and the low number of patients remaining at risk beyond this timepoint (although the CS also states that a plateau would be expected with further follow-up). The EAG agrees that there is uncertainty around

longer-term DFS rates, but notes that no further data-cuts of DFS in ADAURA are expected. Similarly, in the stage II–IIIA subgroup, the percentage of patients in the osimertinib group who were alive and disease-free at 48 months compared with placebo were [redacted] versus [redacted].[48] Comparable benefits in favour of osimertinib versus placebo were also observed in the stage IB subgroup (DFS rate for osimertinib and placebo at 48 months: 80% versus 59%, respectively).[48]

Table 13: ADAURA, DFS in the overall population and subgroups by assessment timepoints (adapted from CS, Table 12 and Herbst *et al.*, 2023)

% (95% CI)	Osimertinib	Placebo
Overall population		
n	339	343
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
Stage II–IIIA subgroup		
N	233	237
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
Stage IB subgroup		
N	106	106
36 months	87 (78, 92)	68 (58, 76)
48 months	80 (70, 87)	59 (48, 68)
60 months	78 (67, 86)	53 (42, 63)

CI - confidence interval; N - number

Summary of median DFS estimates and hazard ratios for DFS (DCO April 2022)

Overall population: At the final DFS analysis (DCO April 2022), median DFS in the osimertinib group compared with the placebo group was 65.8 months and 28.1 months, respectively.[48] Compared with placebo, treatment with osimertinib reduced the risk of disease recurrence or death by 73% (hazard ratio [HR] 0.27; 95% CI 0.21 to 0.34; *p*=not reported [NR]) (see Figure 2).

Stage II-IIIA subgroup: In the final analysis, the median DFS in the osimertinib group was 65.8 months compared to 21.9 months in the placebo group.[48] Compared with placebo, osimertinib resulted in a 77% reduction in risk of disease recurrence or death (HR 0.23; 95% CI 0.18 to 0.30; *p*=NR), respectively (see Figure 3).

Stage IB subgroup: Kaplan-Meier plots of DFS were provided as part of the company's clarification response[42] (question B4; see Figure 4). The company's clarification response noted a treatment benefit in favour of osimertinib in this subgroup which was consistent with findings in the overall population, but stated that the analysis was "*not powered for statistical significance*". The reduction in the risk of recurrence or death in the stage IB subgroup was 59% (HR 0.41; 95% CI 0.23 to 0.69; *p*=NR).

The CS[2] states that *p*-values were not reported because testing for statistical significance was not performed for the final DFS analysis in the study protocol.[2, 49] The EAG notes that the benefit of osimertinib appears to be greater in patients with stage II-IIIA NSCLC compared with patients with stage IB disease.

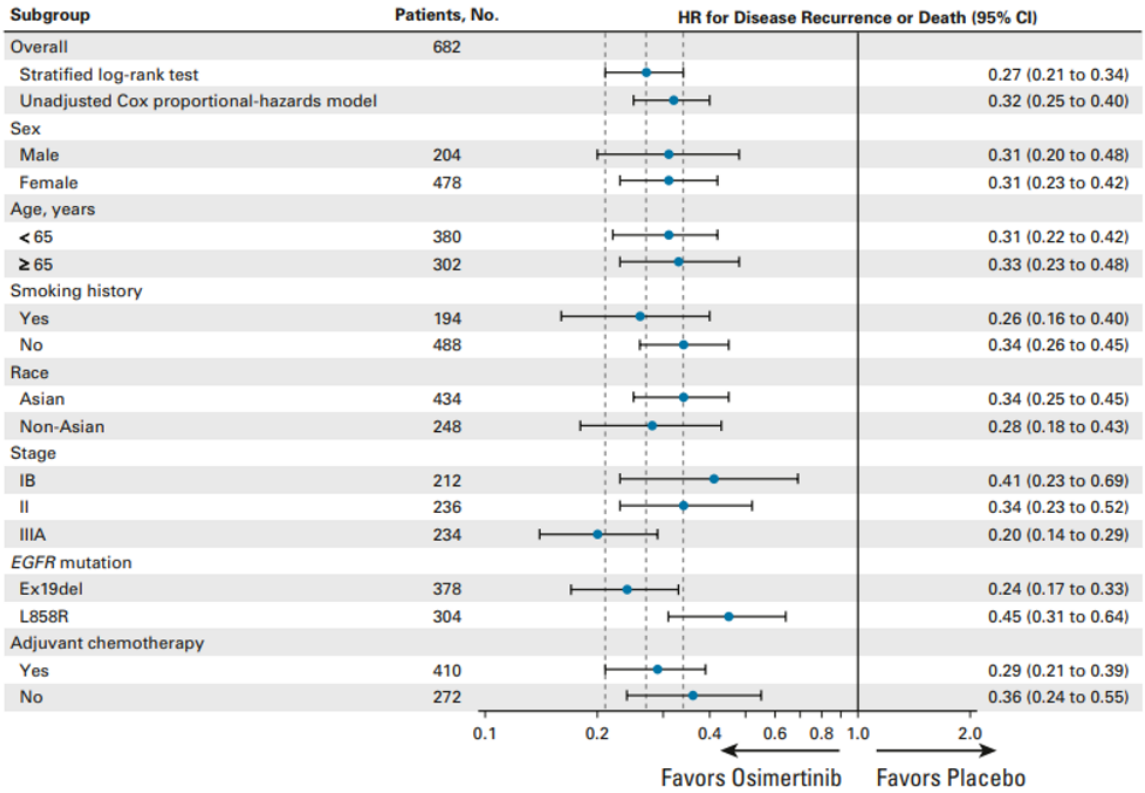
Restaging of patients

Patients in ADAURA[48] had post-surgical pathological staging based on the 7th edition of the AJCC staging system, which has now been superseded by the 8th edition. The 8th edition of the AJCC staging system was used for staging of patients in the supporting SACT dataset.[50] The CS[2] (Section 2.6.1.1) highlights that the re-staging of patients using the 8th edition of the AJCC staging system showed consistency across NSCLC stages in those enrolled in ADAURA (CS,[2] Table 11). The CS[2] notes that at the final DFS analysis (DCO April 2022), HRs for each disease stage remained largely consistent between the 7th and 8th editions of the AJCC staging system.[51] In their response to clarification question B5,[42] the company provided Kaplan-Meier plots of DFS by stage (IB/II/IIIA) comparing each of the two staging editions. The EAG agrees with the company that there is evidence of consistency in staging and treatment effect between the 7th and 8th editions. The EAG's clinical advisors also suggested that prognosis based on the AJCC 7th and 8th editions in the relevant populations is likely to be comparable.

Subgroup analyses for DFS by disease stage

A forest plot summarising the results of subgroup analyses of DFS in ADAURA[48] based on the April 2022 DCO is presented in Figure 5. The CS[2] notes a treatment benefit in favour of osimertinib across all subgroups, regardless of prior adjuvant chemotherapy use.

Figure 5: Subgroup analysis of DFS in ADAURA, overall population (reproduced from CS, Figure 8)



HR - hazard ratio; CI - confidence interval; DFS - disease-free survival; EGFR - epidermal growth factor receptor

Sensitivity analysis of DFS

The CS[2] states that sensitivity analyses were not repeated for the final analysis (DCO April 2022). The CS states that sensitivity analyses on DFS in the overall population and the stage II-IIIA subgroup at the interim analysis (DCO January 2020) noted that:

[redacted]

4.2.6.2 Secondary efficacy outcomes

4.2.6.2.1 CNS disease-free survival

Central nervous system disease-free survival (CNS DFS) was a pre-specified exploratory endpoint in the ADAURA trial.[36] The outcome was defined as CNS disease recurrence or death by any cause. The CS[2] (Section B.2.6.1.2) presents outcomes for the overall population and the stage II-IIIA subgroup at the final DCO of April 2022 (see Table 14). Kaplan-Meier plots of CNS DFS in the overall population and the stage II-IIIA subgroup are presented in Figure 6; an equivalent plot for the stage IB subgroup was not available (see clarification response,[42] question B4).

Table 14: ADAURA, summary of CNS DFS events (adapted from CS, Table 13)

Overall population	**Osimertinib, N=339**	**Placebo, N= 343**
CNS recurrence, N (%)	20 (5.9)	38 (11.1)
Death, N (%)	5 (1.5)	12 (3.5)
Any CNS DFS event, N (%)	25 (7.4)	50 (14.6)
HR (95% CI)	0.36 (0.23, 0.57, *p*=NR)	
Stage II–IIIA population	**Osimertinib, N=233**	**Placebo, N=237**
CNS recurrence, N (%)	18 (7.7)	32 (13.5)
Death, N (%)	4 (1.7)	9 (3.8)
Any CNS DFS event, N (%)	22 (9.4)	41 (17.3)
HR (95% CI)	0.24 (0.14, 0.42, *p*=NR)	

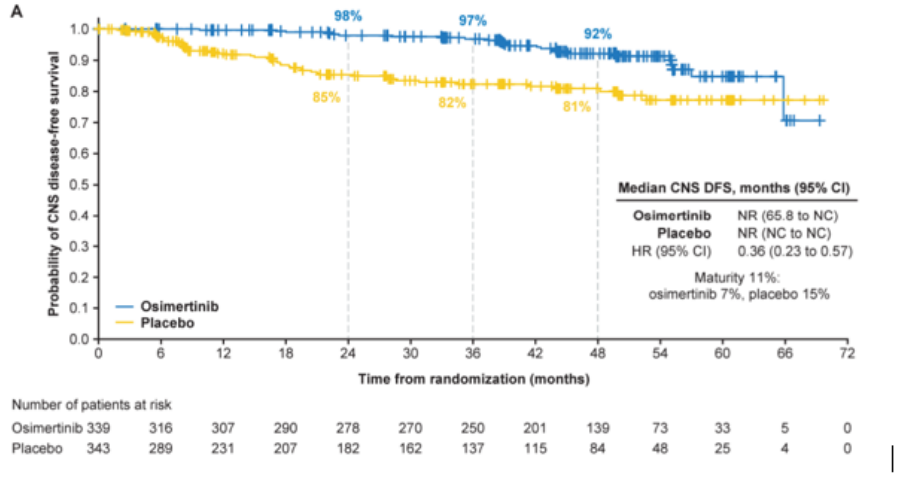
CI - confidence interval; CNS - central nervous system; DFS, disease-free survival; HR - hazard ratio; N – number; NR – not reported

The CS[2] (Section B.2.6.1.2) notes that the results of the updated analysis were comparable to those derived from the earlier DCO and that most CNS recurrences in the osimertinib group occurred after patients had completed their allocated treatment.[48] Fewer CNS DFS events were observed in the osimertinib group compared to the placebo group (DCO April 2022) in both the overall population (7%, n=25 patients versus 15%, n=50 patients, respectively) and in the stage II-IIIA subgroup (9%, n=22 patients versus 17%, n=41 patients, respectively).[2,48] Compared with placebo, osimertinib demonstrated a 64% reduction in the risk of CNS DFS (HR 0.36; 95% CI 0.23, 0.57, *p*=NR) in the overall population and a 76% reduction (HR 0.24; 95% CI 0.14, 0.42 *p*=NR) in the stage II–IIIA subgroup.[2]

Relevant data on CNS DFS for the stage IB population were not presented in the CS.[2] The company confirmed that there was no CNS DFS Kaplan-Meier plot for this subgroup (see clarification response,[42] question B4). The company's clarification response further explained that *p*-values for the available CNS DFS data were missing because the analyses were not powered for statistical significance.

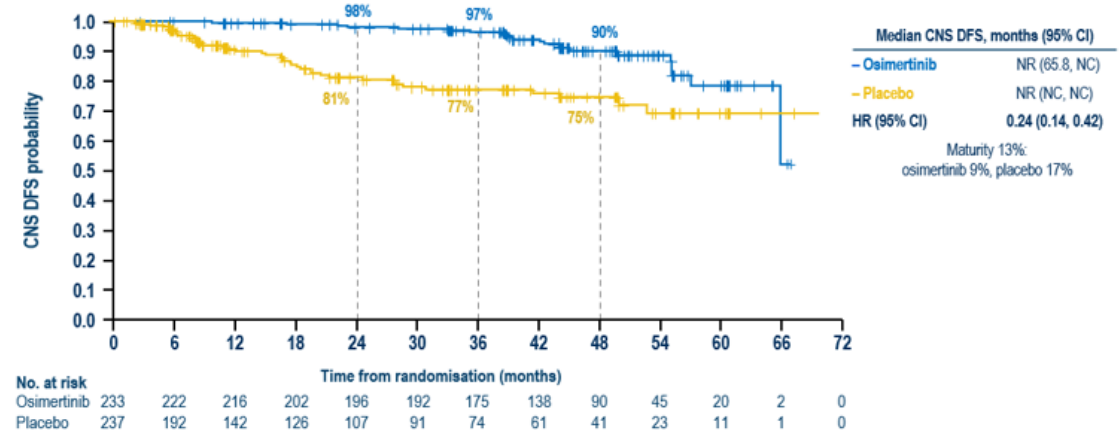
Figure 6: Kaplan-Meier plots of CNS DFS in ADAURA (reproduced from CS, Figures 9 and 10)

Kaplan-Meier plot of CNS DFS in ADAURA study; overall population, post hoc updated analysis



CI - confidence interval; CNS - central nervous system; DFS - disease-free survival; NC - not calculable; NR - not reached. Source: Herbst et al, 2023

Kaplan-Meier plot of CNS DFS in ADAURA study; stage II-IIIA population, post hoc updated analysis



CI - confidence interval; CNS - central nervous system; DFS - disease-free survival; NC - not calculable; NR - not reached. Source: Herbst et al, 2023

4.2.6.2.2 Type and timing of disease recurrence

The CS[2] (Section B.2.6.1.2) notes that treatment with osimertinib was associated with similar rates of local recurrence (12%) and regional recurrence (13%), whereas distant recurrence (31%) and locoregional recurrence (23%) were the most common types observed in the placebo arm. At the final analysis (DCO April 2022), disease recurrence was observed in 27% of patients in the osimertinib group and 60% of patients in the placebo group. The CS[2] (Section B.2.6.1.2) states that the most frequently reported sites of disease recurrence in the ADAURA trial arms were the lung (osimertinib versus placebo: 39 patients [12%] versus 90 patients [26%]) and the CNS (osimertinib versus placebo: 22 patients [6%] versus 39 patients [9%]).[48] Table 15 summarises outcomes from ADAURA on types of disease recurrence and the location of the first site of recurrence.

Table 15: ADAURA, types of recurrence and first site of recurrence (adapted from CS, Tables 14 and 15)

Overall population, n (%)	Osimertinib N=339	Placebo N= 343
Type of disease recurrence		
Disease recurrence	93 (27.4)	205 (59.8)
Local/regional only	42 (12.4)	78 (22.7)
Distant only	45 (13.3)	107 (31.2)
Local/regional and distant	6 (1.8)	20 (5.8)
Location of first site of recurrence (reported in >5% of patients in either treatment arm)		
Lung	39 (12)	90 (26)
CNS	22 (6)	39 (11)
Lymph nodes	19 (6)	59 (17)
Bone	13 (4)	32 (9)
Pleura	5 (1)	22 (6)

CNS - central nervous system; N - number

4.2.6.2.3 Overall survival

Data relating to OS[2] (DCO January 2023) are presented in Table 16, Figure 7 and Figure 8. The median follow-up for OS in the overall population (stage IB-IIIA) was 60.4 months in the osimertinib arm and 59.4 months in the placebo arm at the time of the final OS DCO of January 2023. The planned final analysis was scheduled when OS data maturity was 20%. Numerically, more patients in the osimertinib group were alive at the 5-year timepoint compared with the placebo group in the overall population (OS data maturity level of 18%: 88% versus 78% alive, respectively) and in the stage II-III population (OS data maturity level of 21%: 85% versus 73% alive, respectively). A statistically significant reduction in the risk of death of 51% was observed for osimertinib compared with placebo in the overall population (HR 0.49; 95% CI 0.34, 0.70, p<0.0001) and in the stage II-IIIA subgroup (HR 0.49; 95% CI 0.33, 0.73, p<0.0001). A 56% reduction of risk of death (HR 0.44; 95% CI 0.17, 1.02, p=NR) was observed in the stage IB subgroup (Figure 8). The EAG notes that the OS outcomes for all populations in ADAURA are subject to uncertainty due to high levels of censoring.

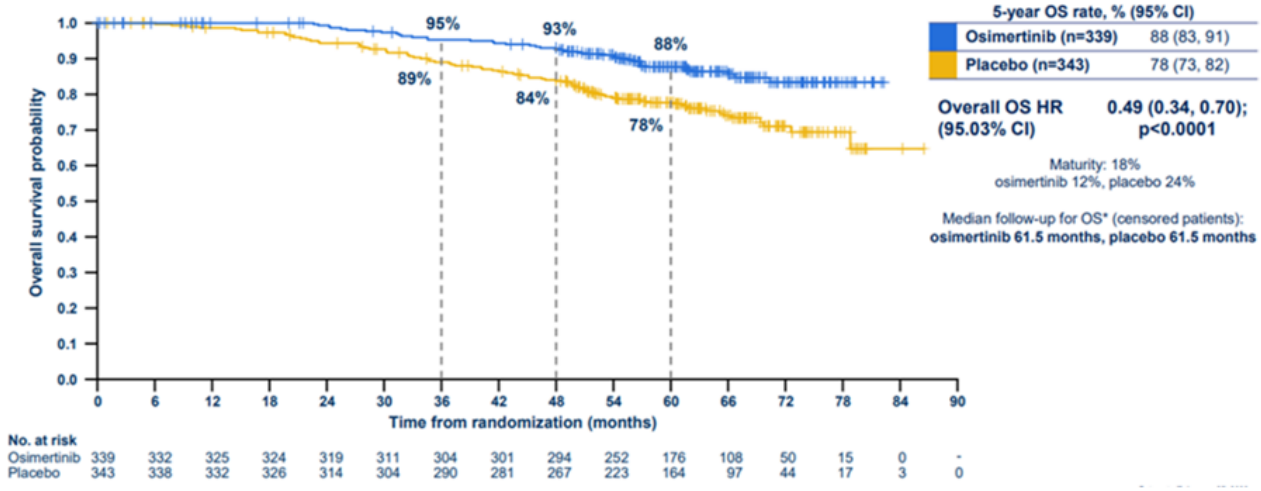
Table 16: ADAURA, five-year overall survival in study populations (adapted from CS, Figures 11 and 12; Tsuboi *et al*., 2023, Figures 2 and 3)

Population	Treatment group	N	Patients alive at 5 years (%)	HR for death (95% CI)
Overall population	Osimertinib	339	88	0.49 (0.34, 0.70) p<0.0001
	Placebo	343	78	
Stage II–IIIA subgroup	Osimertinib	233	85	0.49 (0.3, 0.73) p<0.001
	Placebo	237	73	
Stage IB subgroup	Osimertinib	106	94	0.44 (0.17, 1.02)*
	Placebo	106	88	
Stage II subgroup	Osimertinib	118	85	0.63 (0.34, 1.12)*
	Placebo	118	78	
Stage IIIA subgroup	Osimertinib	115	85	0.37 (0.20, 0.64)*
	Placebo	119	67	
Overall population, with prior adjuvant chemotherapy**	Osimertinib	203	87	0.49 (0.30, 0.79)*
	Placebo	207	77	
Overall population, without prior adjuvant chemotherapy**	Osimertinib	136	88	0.47 (0.25, 0.83)*
	Placebo	136	79	

**p-value, not reported*
***Adjuvant postoperative chemotherapy (if administered, according to physician and patient choice) before randomisation was permitted but not mandatory.*
HR - hazard ratio; CI - confidence interval; N - number

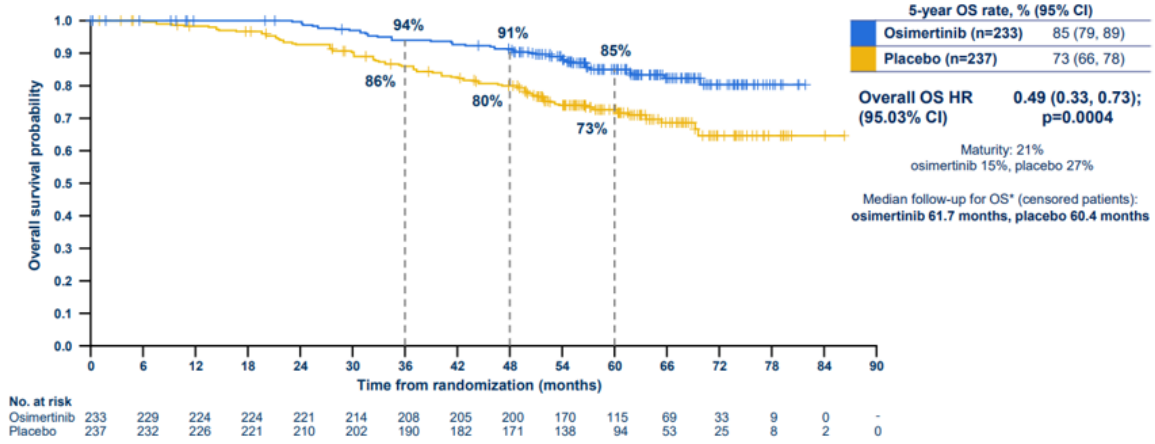
Figure 7: Kaplan-Meier plots of OS in ADAURA - updated analysis (DCO January 2023) in the overall population and the stage II-IIIA subgroup (reproduced from CS, Figure 11 and Figure 12)

Overall population



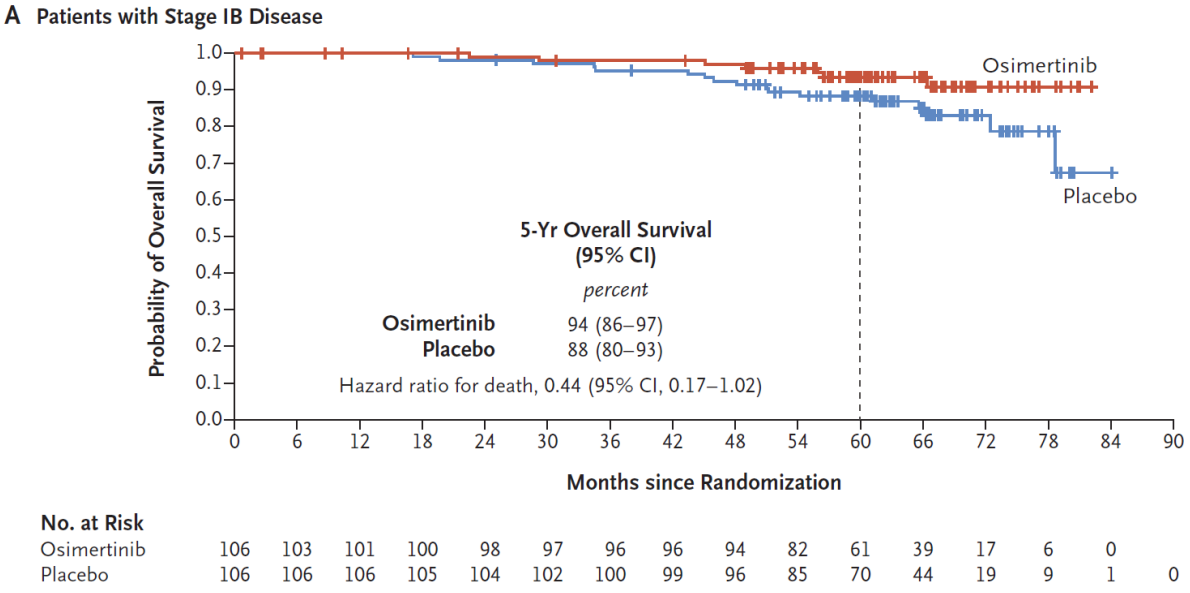
**Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.*
CI - confidence interval; DCO - data cut-off; HR, hazard ratio; OS - overall survival.

Stage II–IIIA subgroup



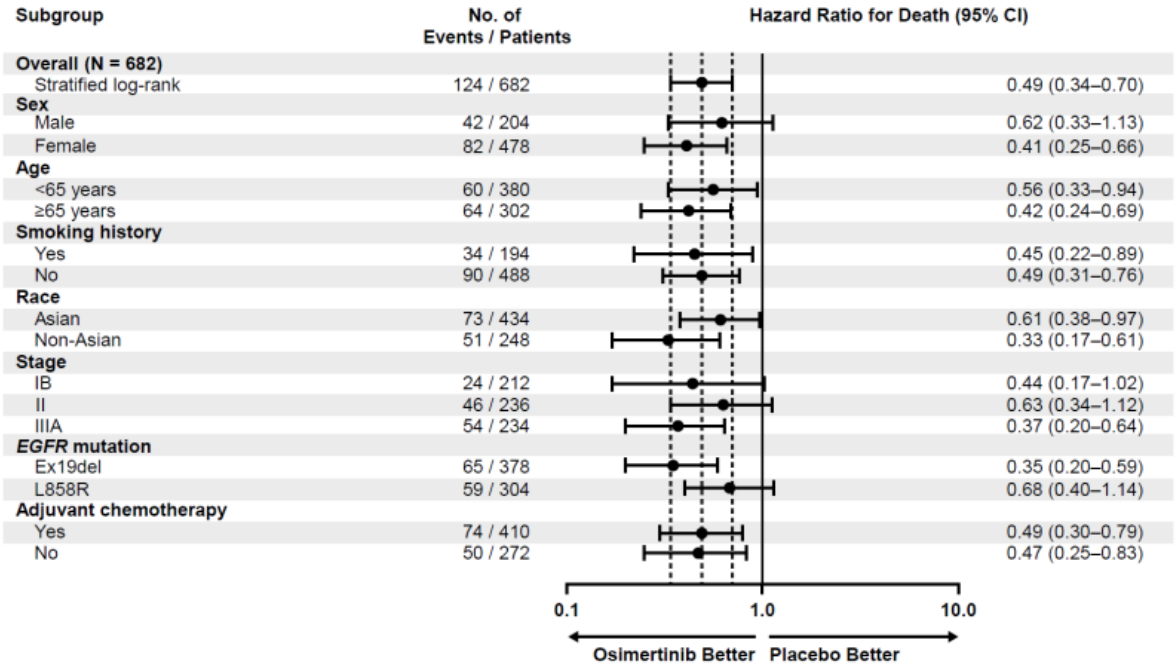
**Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.*
CI - confidence interval; DCO - data cut-off; HR, hazard ratio; OS - overall survival.

Figure 8: Kaplan-Meier plots of OS in ADAURA - updated analysis (DCO January 2023) in the stage IB subgroup



The CS[2] (Section B.2.6.1.2) reports subgroup analyses of OS for the overall population only. Figure 9 indicates an OS benefit in favour of osimertinib compared to placebo across all subgroups, including amongst those patients who received prior chemotherapy and those who did not.[2]

Figure 9: Subgroup analysis of overall survival in ADAURA, overall population (reproduced from CS, Figure 13)



CI - confidence interval; DCO - data cut-off; OS - overall survival.

4.2.6.3 Health-related quality of life

HRQoL in ADAURA[36] was measured using the 36-Item Short Form Survey (SF-36) version 2. The questionnaire was administered at baseline, Day 1 (pre-dose), at 12 weeks, 24 weeks and then every additional 24 weeks from randomisation (±7 days) until treatment completion (3 years) or discontinuation. HRQoL data were not collected following disease relapse. The CS[2] states that results for SF-36 were originally generated at the January 2020 DCO, and were subsequently updated at the April 2022 DCO.

The primary outcome measures of interest were time to deterioration in aggregated summary scores for the physical component score (PCS) and mental component score (MCS). The CS[2] does not provide the data for the PCS and MCS for the updated DCO (April 2022) but states that: [redacted]

The CS[2] also summarises outcomes in clinically meaningful deteriorations in the stage II-IIIA subgroup. The CS notes that: [redacted]

[redacted]

Section B.3.4.2 of the CS[2] also reports the SF-36 in ADAURA mapped to the Euroqol 5-Dimensions 3-Level (EQ-5D-3L) using an algorithm reported by Rowen *et al.*[52] (see Table 17). Individual domain scores of the EQ-5D index were not reported in the CS. Overall mapped EQ-5D-3L scores were similar between the osimertinib and placebo groups, and slightly increased over time.

Table 17: ADAURA, mean EQ-5D scores (reproduced from CS, Table 32)

Time point	Treatment group	N	Mean utility	SD
Baseline	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
Day 1	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
12 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
24 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
48 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
72 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
96 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
120 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
144 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
156 weeks (EOT)	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]

EOT - end of treatment; SD - standard deviation; Tx - treatment

4.2.7 Safety

The safety evidence for osimertinib presented in Section B.2.10 of the CS[2] focuses on data from ADAURA.[48] The safety analyses included AEs with an onset date on or after the date of the first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent anticancer therapy (see clarification response,[42] question B8). AE severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) classification. An updated safety analysis of treatment exposure and AEs was performed at the final analysis of DFS (DCO April 2022), when all patients had completed or discontinued the trial regimen. The CS[2] reports that in ADAURA,[48] the median duration of treatment exposure in the overall population was 35.8 months in the osimertinib group and 25.1 months in the placebo group at the April 2022 DCO. Actual median exposure, which takes dose interruptions into account, was [redacted] in the osimertinib arm. Overall, [redacted] of patients in the osimertinib group and [redacted] of patients in the placebo group completed the full 3 years of treatment.

The proportions of patients who received adjuvant chemotherapy were similar across the two treatment groups, at approximately 60%. Among these, 25% vs 28% had stage IB, 70% vs 73% had stage II, and 81% vs 78% had stage IIIA NSCLC in the osimertinib and placebo groups, respectively.

Overview of AEs in ADAURA

The CS[2] states that no new safety concerns were reported at the DCO of April 2022 or at the final analysis (DCO January 2023) of ADAURA.[36] In total, 98% of patients in the osimertinib group and 90% in the placebo group reported ≥1 AE during the trial. More AEs considered to be related to treatment were noted in the osimertinib group compared with the placebo group (91% versus 58% respectively, see Table 18). Of these, serious adverse events (SAEs) were reported by 20% of patients receiving osimertinib and 14% of patients receiving placebo. In the CS[2] (Table 17), the proportions of any grade of AEs and Grade ≥3 AEs were presented according to the frequency of presentation (i.e., occurring in ≥10% of patients) in each treatment group. In the osimertinib group, 11% of patients had treatment-related Grade≥3 AEs compared with 2% in the placebo group.

The CS[2] reports that early treatment discontinuation in the osimertinib group was most frequently due to an AE (12.2%), followed by patient decision (10.1%), or disease recurrence (9.8%). In the placebo group, discontinuation was most frequently due to disease recurrence (50.1%), followed by patient decision (3.5%) or due to an AE (3.2%). The proportions of patients with an AE leading to dose reduction, interruption, and treatment discontinuation were higher in the osimertinib group and were as follows for the osimertinib and placebo groups, respectively: dose reductions in 12% vs. 1% of patients; dose interruptions in 27% vs. 13% of patients; and treatment discontinuation in 13% vs. 3% of patients.

In total, three patients died due to AEs. One of these deaths occurred in the osimertinib group and was due to respiratory failure attributed to COVID-19. The remaining two deaths occurred in the placebo group – one was due to pulmonary embolism and the other was due to an unknown cause. None of these deaths were considered to be treatment-related.

Table 18: ADAURA, summary of AEs (reproduced from CS, Table 16 and clarification response, question B8)

AEs, N (%)	Osimertinib (N=337)	Placebo (N=343)
Any AE AEs considered causally-related to treatment† AEs of CTCAE Grade 3 or higher considered causally-related to treatment	330 (98) 308 (91) 36 (11)	309 (90) 199 (58) 7 (2)
Any SAE SAEs considered causally reported to treatment†	68 (20) 10 (3)	47 (14) 2 (1)
Change in treatment/trial continuation due to AEs Trial regimen discontinuation Dose interruption Dose reduction	 43 (13) 91 (27) 42 (12)	 9 (3) 43 (13) 3 (1)
Any AE with outcome of death AEs with outcome of death considered causally-related to treatment†	1 (<1) 0	2 (1) 0

DCO April 2022; † As evaluated by the trial investigator
AE - adverse event; CTCAE - Common Terminology Criteria for Adverse Events; SAE - serious adverse event

Most common AEs in ADAURA

The most frequently reported AEs (with a frequency of ≥10% of patients in either treatment group) in the osimertinib group were diarrhoea, paronychia (infection of the skin around the nails), dry skin, pruritis (itch), and cough (see Table 19). Within the placebo group, the most frequently reported AEs were diarrhoea, cough, upper respiratory tract infection, and arthralgia. The proportions of patients experiencing any grade and Grade ≥3 diarrhoea, any grade paronychia, dry skin, pruritis and stomatitis (sore mouth) were much higher in the osimertinib group.

Table 19: ADAURA, most common AEs, ≥10% of patients in either treatment group (reproduced from CS, Table 17)

AEs, n (%)	Osimertinib (N=337)		Placebo (N=343)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	159 (47)	9 (3)	70 (20)	1 (<1)
Paronychia	92 (27)	3 (1)	5 (1)	0
Dry skin	84 (25)	1 (<1)	23 (7)	0
Pruritis	70 (21)	0	30 (9)	0
Cough	66 (20)	0	61 (18)	0
Stomatitis	59 (18)	6 (2)	15 (4)	0
Upper respiratory tract infection	53 (16)	2 (1)	37 (11)	0
Nasopharyngitis	50 (15)	0	36 (10)	0
Decreased appetite	48 (14)	2 (1)	13 (4)	0
Dermatitis acneiform	41 (12)	0	16 (5)	0
Mouth ulceration	39 (12)	0	10 (3)	0
Weight decreased	35 (10)	2 (1)	9 (3)	0
Nausea	34 (10)	1 (<1)	20 (6)	0
Rash	33 (10)	0	12 (3)	0
Arthralgia	23 (7)	0	37 (11)	0
Headache	26 (8)	0	34 (10)	0

DCO April 2022; AE - adverse event

AEs of special interest in ADAURA

AEs of special interest included ILD and cardiac AEs. The CS[2] reports that 11 patients had ILD events which were of a mild or moderate severity, and all of these were in the osimertinib group (3% of the intervention group). Cardiac events (including ejection fraction decrease, cardiac failure, pulmonary oedema, and cardiomyopathy) were reported in 19 patients (6%) treated with osimertinib and 9 patients (3%) treated with placebo; most were Grade 1 or 2 events.

4.2.8 Additional data from SACT

The CS[2] presents data from the ADAURA trial[36] as the primary source of clinical effectiveness evidence. This is supported by the presentation of real-world data on adjuvant osimertinib use in England during the period of managed access through the CDF, based on the SACT dataset. This secondary source of information is presented in Section B.2.6.2 of the CS and in CS Appendix R.[37] The available data from SACT are summarised in the subsequent sections.

Managed access within the CDF

In January 2022, NICE published a positive recommendation for adjuvant treatment with osimertinib through the CDF. Eligible patients included adults with stage IB to IIIA NSCLC after complete tumour resection whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. CS Appendix R[37] notes the prospect of addressing areas of uncertainty identified in TA761[20] through further data collection in ADAURA and additional data collection within the CDF. Areas of uncertainty listed in CS, Appendix R[37] (page 307) were as follows:

- *"what extent a benefit in disease-free survival translates into a benefit in overall survival"*
- *"the extent of the cure proportion, and the cure time point"*
- *"the impact of the 3-year stopping rule"*
- *"the proportion of patients that would be retreated with osimertinib."*

Methods and results: SACT

CS Appendix R[37] states that: "*Patients eligible for treatment with osimertinib through the CDF were adults after complete resection of stage IB to IIIA NSCLC (according to the 8th edition of AJCC TNM), whose tumours had EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.*"

The CS[2] and CS Appendix R[37] report outcomes from SACT relating to the use of adjuvant osimertinib in NHS clinical practice in England. The SACT dataset includes 143 patients and covers applications for adjuvant osimertinib identified through the Blueteq system over the period 30th November 2021 to 31st December 2022.

Patient characteristics, treatment duration and overall survival: SACT

CS Appendix R[37] presents information on patient characteristics, treatment duration and OS; these data are summarised together in Table 20. The patients included in the SACT dataset were mostly female (77%) and were aged ≥50 years (94%). In ADAURA,[36] the study population had a median age of 64 years and 68% were female. 73% of patients in SACT had a known PS of 0 to 1, although data on the PS of the remaining 27% of patients were missing. The stage distributions of patients in SACT and ADAURA were similar, with prior chemotherapy use notably lower in SACT compared with ADAURA (27% vs 60%). The EAG's clinical advisors suggested that the difference in rates of chemotherapy use likely relates to differences between the patient populations, with SACT containing more patients who would otherwise not be suitable for any adjuvant treatment.

Median treatment duration in SACT was shorter than in ADAURA (14.7 months versus 35.8 months), but this is due to 80% of patients in SACT still receiving treatment at the time of the DCO for the analysis. CS Appendix R[37] presents Kaplan-Meier plots of treatment duration and OS; however, these are limited by short follow-up and therefore are not reproduced here. Median follow-up and data maturity for OS was 9.3 months and 6.2% (9 events in 143 patients), respectively. Median OS was not reached for patients in the SACT dataset. Sensitivity analyses presented for those patients with a treatment duration of at least 6 months were in line with the analysis of the entire cohort. The EAG notes that the SACT dataset provides no data on osimertinib re-treatment rates or cure rates.

Table 20: Comparative summary of patient characteristics, treatment duration and overall survival from the SACT dataset and the ADAURA trial (adapted from CS, Table 9 and Figure 11, and CS Appendix R, page 308, Tables 68 and 69)

	SACT		ADAURA osimertinib arm	
Patient characteristics				
Setting	UK		212 sites in 24 countries[*]	
Patients that received osimertinib	143		339	
Females, N (%)	110 (77%)		230 (68%)	
Age≥50 years, N (%)	135 (94%)		Median = 64, range 30–86	
Performance status 0-1, N (%)	104 (73%); *27% missing*		339 (100%)	
Race, N (%)				
White	Not reported		122 (36%)	
Asian	Not reported		216 (64%)	
Other	Not reported		1 (<1)	
Stage of disease, N (%)	*1% missing*			
Stage IB disease	41 (29%)		102 (30%)	
Stage IIA disease	19 (13%)		112 (33%)	
Stage IIB disease	39 (27%)			
Stage IIIA disease	33 (23%)		108 (32%)	
Tumour specimen (biopsy or surgical), N (%)	*1% missing*			
Exon 19 deletion	77 (54%)		185 (55%)	
Exon 21 substitution mutation	65 (45%)		153 (45%)	
Prior chemotherapy %	39 (27%); *1% missing*		202 (60%)	
Treatment duration				
Median follow-up	6.7 months			
Median treatment duration	14.7 months[**]		35.8 months[***]	
Patients on treatment at 6 months	116 (81%)		332 (98%)	
Patients on treatment at 12 months	107 (75%)		325 (96%)	
No longer on treatment at DCO	29 (20%)		339 (100%)[§]	
Ongoing treatment at DCO	114 (80%)		0 (0%)	
Overall survival				
DCO	April 2023		January 2023	
Median follow-up time	9.3 months		61.7 months[§§]	
Data maturity	6.2%		12%[§§§]	
Median OS	Not reached		Not reached	
OS at specific timepoints	6-month OS	96%	60-month OS	88%
	12-month OS	92%		

[*] *UK setting(s), unknown*
[**] *Calculated from the start of a patient's treatment to their last known treatment date in SACT.*
[***] *Described as median duration of treatment exposure.*
[§] *All patients had completed or discontinued the study treatment at DFS DCO April 2022.*
[§§] *Follow-up for stage II to IIIA population (Tsuboi et al., 2023)[49]*
[§§§] *Data maturity for the entire trial population was 18% and 21% for stage II to IIIA population*
DCO - data cut-off; OS - overall survival, n - number; SACT - Systemic Anticancer Therapy

4.3 Discussion

4.3.1 Summary of clinical effectiveness evidence

The CS[2] focuses on the updated analysis of the ADARUA trial as the primary source of evidence for adjuvant osimertinib, based on the latest DCOs of the 11th April 2022 for DFS and the 27th January 2023 for OS.[48, 49] Supporting evidence is presented from the SACT dataset.[37] Treatment duration in ADAURA was planned for 3 years or until disease recurrence or fulfilment of a discontinuation criterion. The trial was unblinded two years early due to overwhelming efficacy with osimertinib for DFS. The results of the first interim analysis were presented to NICE in TA761.[20]

Based on the updated DCOs, ADAURA reported a DFS benefit for adjuvant osimertinib in the overall population (HR 0.27; 95% CI 0.21, 0.34), the stage II-IIIA subgroup (HR 0.23; 95% CI 0.18, 0.30), and the stage IB subgroup (HR 0.41; 95% CI 0.23, 0.69). Compared with placebo, osimertinib also improved CNS DFS in the overall population (HR 0.36; 95% CI 0.23, 0.57) and in the stage II-IIIA subgroup (HR 0.24; 95% CI 0.14, 0.42). Results were not available for the stage IB subgroup.[48] Osimertinib was associated with a statistically significant reduction in the risk of death in the overall population (HR 0.49; 95% CI 0.34, 0.70, $p<0.0001$), the stage II-IIIA subgroup (HR 0.49; 95% CI 0.33, 0.73, $p<0.0001$), and the stage IB subgroup (HR, 0.44; 95% CI 0.17, 1.02, p=NR). Subgroup analysis demonstrated consistent benefits in DFS and OS in favour of adjuvant osimertinib, regardless of prior adjuvant chemotherapy use.

In the overall population, recurrences in the osimertinib group included: local/regional only 12%; distant only 13% and local/regional and distant 2%. The number of recurrences in the placebo group was higher: local/regional only 23%; distant only 31% and local/regional and distant 6%. The lungs were the most common location for the first site of recurrence in both treatment groups (osimertinib versus placebo: 12% versus 26%).

Median OS was not reached for patients in the SACT dataset (median follow-up, 9.3 months; data maturity 6.2%). Eighty percent of patients in SACT were still receiving treatment at the time of the DCO for the analysis. The SACT dataset did not provide any additional data on cure rates or on the proportion of patients who receive adjuvant osimertinib and go on to receive re-treatment with osimertinib for metastatic relapse.[37]

Overall, there remains uncertainty around the longer-term benefits of adjuvant osimertinib on DFS and OS, including the potential for curative outcomes. The EAG notes that further data-cuts on DFS are not anticipated and the DCO of April 2022 reflects the primary (final) analysis.

4.3.2 Summary of safety evidence

The safety evidence for adjuvant osimertinib presented in the CS[2] is based on the ADAURA RCT.[48, 49] SAEs were reported in 20% and 14% of patients in the osimertinib and placebo groups, respectively, of which 3% and 1% respectively were considered related to treatment. Grade ≥3 AEs considered related to treatment were reported by 11% and 2% of patients in the osimertinib and placebo groups, respectively. Change in treatment/treatment discontinuation due to AEs was required for 52% of patients in the osimertinib group and 16% of patients in the placebo group. The most frequently reported AEs (with a frequency of ≥10% of patients in either treatment group) in the osimertinib group were diarrhoea, paronychia (infection of skin around nails), dry skin, pruritis (itch), and cough. AEs of special interest for osimertinib include ILD or pneumonitis and cardiac AEs. ILD events were reported in 11 (3%) patients treated with osimertinib and 0 patients receiving placebo; all events were mild or moderate in severity. Cardiac AEs (ejection fraction decrease, cardiac failure, pulmonary oedema, cardiomyopathy) were reported in 19 (6%) patients treated with osimertinib and 9 (3%) patients treated with placebo.

Three AE-related deaths occurred in ADAURA - one occurred in the osimertinib group (respiratory failure attributed to COVID-19) and two occurred in placebo group (pulmonary embolism and cause unknown).

5. COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of adjuvant osimertinib for the treatment of adult patients with fully resected, stage IB-IIIA EGFRm NSCLC. Section 5.1 describes and critiques the company's SLR of existing economic analyses of treatments for patients with stage IB–IIIA EGFRm NSCLC following complete tumour resection. Section 5.2 describes the company's economic model and summarises the company's results. Section 5.3 presents the EAG's critical appraisal of the company's original economic model. Section 5.4 briefly summarises and critiques the second updated version of the company's model provided following the clarification round. Section 5.5 presents the methods and results of the EAG's exploratory analyses. Section 5.6 discusses the key issues and uncertainties around the company's economic analysis.

5.1 Summary and critique of the company's review of existing economic analyses

5.1.1 Methods

The company undertook an SLR of existing cost-effectiveness analyses of treatments for patients with stage IB–IIIA EGFRm NSCLC following complete tumour resection, with or without adjuvant chemotherapy. Includable studies were not limited by intervention or comparator. Eligible studies included full economic evaluations, cost-minimisation analyses, and cost analyses. Studies were screened based on their title and abstract by two independent reviewers; disagreements were resolved through the inclusion of a third reviewer. Study data were extracted by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. Studies were quality assessed by one reviewer and checked by a second reviewer using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[53]

The searches for the company's SLR of economic, utility and cost and resource use studies were originally conducted in November 2020 and are reproduced in CS Appendices G, H and I,[37] respectively.[37] All of the core databases (MEDLINE-ALL, Embase, Cochrane Library, and EconLit) were included. The initial phase of searching also included hand searching of reference lists of included studies and systematic reviews, plus proceedings of a number of relevant conference series (see clarification response,[42] question A6). Update searches were conducted in August 2023.

5.1.2 Results

The company's review included a total of four economic evaluation studies,[54-57] all of which were identified from the update search conducted in 2023. The included studies are summarised in Table 21. All four included studies were model-based economic evaluations of treatments for EGFRm NSCLC. Three of the included studies evaluated adjuvant osimertinib versus placebo (active monitoring),[55-57] whereas the fourth study evaluated gefitinib versus adjuvant chemotherapy.[54] Two studies were undertaken in China,[54, 55] one was undertaken in the US[56] and one was undertaken in Canada.[57]

The EAG notes the following observations regarding the company's SLR of existing economic evaluations:

- The company's original 2020 search strategies are designed logically, using subject headings and free text terms, along with filters to identify the eligible study types, though it is regrettable that the free-text strings (which were identical across all three SLRs) did not include the UK spelling of "tumour." For the update searches in August 2023, it appears that a lighter touch was employed, although the reporting is somewhat confusing. In CS Appendix G.2,[37] the company states that they searched the same databases, using the same strategies as in 2020. However, in their response to clarification question A7,[42] the company refers to the use of *"improved search terms"* and *"the inclusion of a wider selection of databases."* The update searches also appear to have placed less emphasis on hand searching for grey literature, apparently based on the assumption that all relevant conference proceedings would have been retrieved via their Ovid search (see clarification response, question A6). This may be the case, but for completeness, it would have been sensible to check. The EAG also notes that the omission of transcripts from the CS[2] and the apparent contradictions between some of the company's statements about the strategies used mean that some uncertainties persist regarding the 2023 update searches. It is possible that the company's approach was indeed fit for purpose, but without greater transparency about the methods, the EAG cannot be assured that it was optimal.
- Whilst CS Appendix G[37] states that the company's search strategy included hand searching of previous HTA submissions, the model used to inform NICE TA761[20] has not been included in the company's review, nor has any other health technology assessment (HTA) agency submission or review relating to adjuvant osimertinib (e.g., those available from the Scottish Medicines Consortium [SMC],[58] the National Centre for Pharmacoeconomics [NCPE],[59] and the Canadian Agency for Drugs and Technologies in Health [CADTH][60]). The reason for the exclusion of these economic analyses is unclear.
- The time horizons applied in the included models ranged from 10 years to 38 years (lifetime). Applying shorter time horizons is unlikely to capture all differences in health outcomes and costs of competing adjuvant treatments for NSCLC.
- The Canadian analysis of adjuvant osimertinib reported by Verhoek *et al.*[57] applies a very similar model structure to that used to inform NICE TA761,[20] based on a state transition approach with five distinct health states defined according to survival status, type of recurrence (local/distant) and first- and second-line treatments in patients with metastatic relapse. The economic model submitted by the company within the current appraisal also applies a similar structure (see Section 5.2.2). The company's clarification response[42] (question C1) highlights

that this approach allows for a more granular representation of the underlying disease and treatment processes compared with the other published models included in the review.

- All four included studies adopted a state transition approach including disease-free and post-relapse/progression health states. All three economic models of adjuvant osimertinib were informed by the ADAURA trial,[36] with post-relapse outcomes informed by the FLAURA trial (osimertinib for untreated advanced EGFRm NSCLC).[39]
- All three models of adjuvant osimertinib included an assumption that some patients are re-treated with osimertinib following distant relapse.
- None of the economic analyses of adjuvant osimertinib included a comparison against adjuvant chemotherapy. The study reported by Li *et al.*[54] compared an alternative TKI (gefitinib) as adjuvant treatment against adjuvant chemotherapy, based on a head-to-head comparison in the ADJUVANT trial.[61]
- The base case analyses presented in the studies of osimertinib used health state utility values sourced from other literature, rather than from ADAURA.[36] Within the study by Verhoek *et al.*,[57] the authors state that this was because there was no direct mapping algorithm available from SF-36 to EQ-5D with the Canadian tariff applied. Mapped utility values from the SF-36 to the SF-12 to the EQ-5D were however considered in scenario analyses.
- Only one of the four studies – Verhoek *et al.*[57] – included an explicit assumption of cure. This model applied a cure timepoint at 5 years for the active monitoring group and at 8 years for the adjuvant osimertinib group. The cure assumption was implemented by assuming that the predicted risk of relapse was reduced by 0% at the end of year 4, increasing linearly to 95% by the final cure timepoint in each group. This is similar to the approach used in the company's current model (see Section 5.2).

Table 21: Summary of studies included in the company's review of published economic evaluations

Study	Publication type	Setting	Population	Intervention/ comparators	Model type	Time horizon	Cure assumptions	Is osimertinib re-treatment included?	Key efficacy sources	HRQoL sources
Lemmon *et al.* (2022)[56]	Full text	US	Resected EGFRm NSCLC, stage IB-IIIA	• Adjuvant osimertinib • Placebo	STM	10 years	None reported	Yes	ADAURA,[36] FLAURA,[39] AURA3[62]	Bodnar *et al.*,[63] Yang *et al.*,[64] Lester-Coll *et al.*,[65] Chouaid *et al.*[66]
Zhou *et al.* (2022)[55]	Full text	China	Resected EGFRm NSCLC, stage IB-IIIA	• Adjuvant osimertinib • Placebo	STM	20 years	None reported. Survival model plot suggests continued risk of recurrence.	Yes - assumes continued osimertinib treatment after progression	ADAURA,[36] FLAURA,[39]	Lu *et al.*,[67] Grutters *et al.*,[68] Chouaid *et al.*[66]
Verhoek *et al.* (2023)[57]	Full text	Canada	Resected EGFRm NSCLC, stage IB-IIIA	• Adjuvant osimertinib • Active surveillance	STM	38 years (lifetime)	Structural cure assumptions at 8 years for osimertinib and 5 years for active surveillance	Yes - re-treatment permitted from 4 years after starting adjuvant osimertinib	ADAURA,[36] FLAURA,[39]	Sources not clearly reported
Li *et al.* (2021)[54]	Full text	China	R0 resected EGFRm NSCLC, stage II-IIIA (N1-N2)	• Gefitinib • Chemotherapy	STM	10 years	None reported	N/a	ADJUVANT[61]	Labbe *et al.*,[69] Brown *et al.*[70]

HRQoL - health-related quality of life; US - United States; EGFRm - epidermal growth factor receptor mutation-positive; NSCLC - non-small cell lung cancer; STM - state transition model; N/a - not applicable

5.2 Summary of the company's submitted economic evaluation

This section describes the methods and results of the company's original submitted model, as described in the CS.[2] Following the clarification process, the company submitted two updated versions of the model which include the correction of several errors identified by the EAG. The company's second updated model and its results are summarised separately in Section 5.4.

5.2.1 Scope of the company's economic analysis

As part of its submission to NICE,[2] the company submitted a fully executable health economic model which was programmed in Microsoft Excel®. The scope of the company's economic analysis is summarised in Table 22. The model compares osimertinib as adjuvant therapy versus active monitoring for patients with completely resected, stage IB-IIIA EGFRm-positive NSCLC. The model uses a state transition (semi-Markov) approach, based on time-to-event data from the ADAURA trial,[36] as well as external data for post-relapse outcomes (the CancerLinQ database,[71] the FLAURA trial,[39] the IMPower150 trial[40] and general population life tables[41]). The economic analysis was undertaken from the perspective of the NHS and Personal Social Services (PSS) over a 37-year (lifetime) horizon. Cost-effectiveness is assessed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Unit costs are valued at 2021/22 prices, with the exception of drugs which are valued at current prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Table 22: Scope of the company's economic analysis

Population	Adults with fully resected, stage IB-IIIA EGFRm-positive NSCLC
Time horizon	37 years (lifetime)
Intervention	Adjuvant osimertinib
Comparator	Active monitoring
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2021/22 (except for drugs which are valued at current prices)

EGFR - epidermal growth factor receptor; NSCLC - non-small cell lung cancer; QALY - quality adjusted life year; NHS - National Health Service; PSS - Personal Social Services

Population

The population included in the company's economic model reflects the overall population of ADAURA[36] (stage IB-IIIA). At model entry, patients are assumed to have a mean age of 63 years and 70% of patients are assumed to be female.

Intervention

The intervention evaluated within the economic analysis is adjuvant osimertinib administered orally at a dose of 80mg once daily. The model includes a stopping rule at three years for all patients receiving adjuvant osimertinib, based on the design of the ADAURA trial.[36] As noted in Section 3.2, the SmPC[32] for osimertinib does not include a formal stopping rule; Section 4.2. of the SmPC states: *"Patients in*

the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied." This implies that osimertinib treatment should be discontinued after three years, although this is not stipulated as part of the marketing authorisation. The EAG's clinical advisors commented that they would discontinue adjuvant treatment with osimertinib after a maximum of three years.

Comparator

The comparator included in the company's model is active monitoring (established clinical management without adjuvant osimertinib). Under this option, patients are assumed to receive monitoring for disease recurrence, with no further active treatment unless the patient experiences loco-regional and/or distant recurrence.

The final NICE scope[33] also lists adjuvant chemotherapy as a comparator for this appraisal. The company's economic model does not include an economic comparison between adjuvant osimertinib (with or without prior adjuvant chemotherapy) versus adjuvant chemotherapy alone. This issue is discussed further in Section 5.3.6.

Downstream treatments following loco-regional or distant relapse

Table 23 summarises the treatment pathways following loco-regional or distant recurrence assumed in the company's model. These pathways are described briefly below.

Table 23: Downstream treatment pathway assumed following adjuvant osimertinib and active monitoring

Model treatment group	Treatment for loco-regional recurrence (LRR)	Re-treatment pathway	First-line treatment for distant metastases (DM1)	Second-line treatment for distant metastases (DM2)
Adjuvant osimertinib (up to 3 years of treatment)	82% receive 4 cycles of PDC plus radiotherapy, 18% receive single-modality radiotherapy	No*	5 cycles of PDC‡	4 cycles of docetaxel§
		Yes†	Osimertinib (until progression or death)	80% receive 5 cycles of PDC‡ 20% receive ABCP¶ (3 cycles carboplatin and paclitaxel, indefinite treatment with atezolizumab and bevacizumab)
Active monitoring		N/a	83% receive osimertinib (until progression or death) 17% receive early TKI (erlotinib, gefitinib or afatinib; until progression or death)	

LRR- loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; PDC - pemetrexed plus cisplatin; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel; TKI - tyrosine kinase inhibitor; N/a - not applicable

** All patients progressing within 4 years and 50% of patients after 4 years since starting adjuvant treatment*

† 50% of patients progressing after 4 years since starting adjuvant osimertinib

‡ Five 21-day cycles correspond to 3.4 model cycles

§ Four 21-day cycles correspond to 2.8 model cycles

¶ Three 21-day cycles of carboplatin and paclitaxel correspond to 2.8 model cycles, although this is subject to a minor error in the model (see Section 5.3.6, critical appraisal point [i])

Treatments for loco-regional recurrence

In both treatment groups, the model assumes that 82% of patients who experience loco-regional recurrence will receive four 21-day cycles of pemetrexed plus cisplatin (PDC) plus radiotherapy (500mg pemetrexed intravenous [IV], 75mg cisplatin IV, plus 20 fractions of radiotherapy given over 28 days). The remaining 18% of patients are assumed to receive single-modality radiotherapy. Surgery is not included as a treatment approach for loco-regional recurrence.

First-line treatments for distant metastases

All patients who experience distant recurrence are assumed to receive active therapy.

In the active monitoring comparator group, 83% of patients who develop distant metastases are assumed to receive osimertinib as first-line treatment in the metastatic setting (80mg daily), with the remaining 17% receiving an alternative "early" TKI (either erlotinib, gefitinib or afatinib). Treatment using any of these TKIs is assumed to continue until disease progression or death.

In the intervention group, all patients who develop distant metastases within four years of starting adjuvant osimertinib are assumed to receive first-line treatment with PDC (500mg pemetrexed IV, 75mg cisplatin IV) over five 21-day cycles or until progression or death. After this 4-year timepoint, 50% of patients who develop distant metastases are assumed to be re-treated with osimertinib as first-line therapy, with the remaining 50% receiving five 21-day cycles of PDC (500mg pemetrexed IV, 75mg cisplatin IV).

Second-line treatments for distant metastases

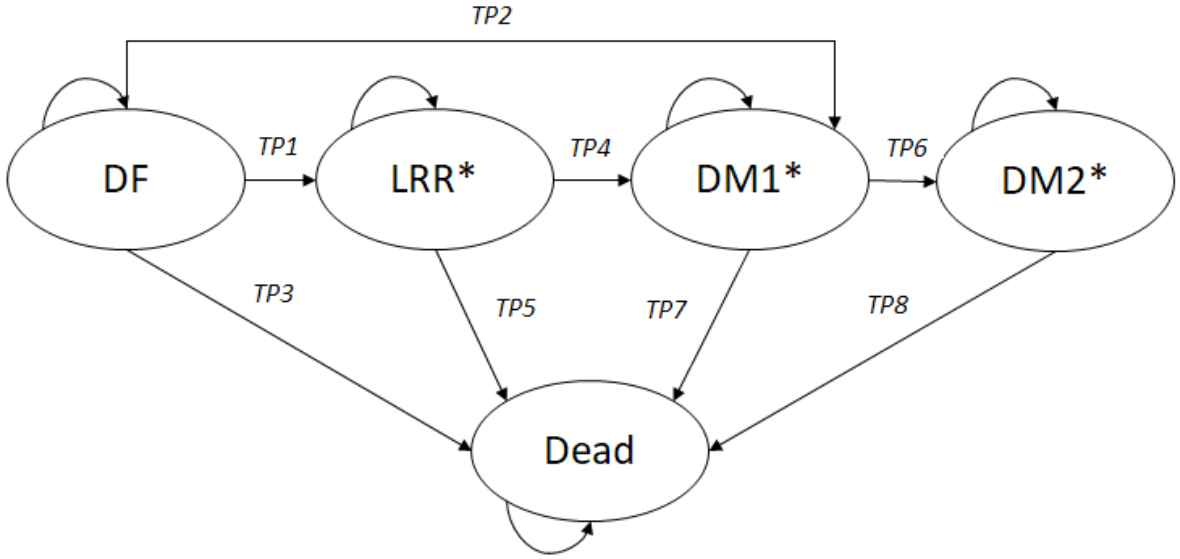
All patients who progress on first-line treatment for distant metastases are assumed to go on to receive second-line treatment. Patients who have previously received PDC as first-line treatment are assumed to receive four 21-day cycles of docetaxel (75mg IV). Eighty percent of those patients who received osimertinib or an early TKI (erlotinib, gefitinib or afatinib) in the first-line metastatic setting are assumed to receive five 21-day cycles of PDC (500mg pemetrexed IV, 75mg cisplatin IV) as second-line treatment. The remaining 20% of patients receive treatment with ABCP as second-line treatment (3 cycles of carboplatin and paclitaxel, treatment with atezolizumab and bevacizumab until death).

5.2.2 Model structure and logic

The company's economic model adopts a cohort-level semi-Markov approach, with some adjustment for competing risks. The model structure is comprised of five health states: (i) disease-free (DF); (ii) loco-regional recurrence (LRR); (iii) first-line treatment for distant metastases (DM1); (iv) second-line treatment for distant metastases (DM2), and (v) dead (see Figure 10). The model includes multiple distinct DM1 and DM2 health states to reflect the alternative treatment sequences described in Table

23. Overall, the model structure is very similar to the model used to inform NICE TA761[20] and the published model described by Verhoek *et al.*[57]

Figure 10: Company's model structure



DF - disease-free; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; TP - transition probability
**Sub-models for intermediate health states use tunnel states to allow event risks to be conditional on time since state entry. In the adjuvant osimertinib group, separate DM1 and DM2 sub-models are applied for patients who can or cannot receive re-treatment with osimertinib as first-line for distant metastases. In the active monitoring group, separate DM1 and DM2 sub-models are applied for patients who receive osimertinib or an early TKI as first-line therapy for distant metastases.*

The model logic operates as follows. Patients enter the model in the DF state and receive treatment with adjuvant osimertinib or active monitoring. Patients in the intervention group receive adjuvant osimertinib for up to three years, based on the observed TTD data from ADAURA[36] (note – this is not structurally linked to any model health state). The following health state transitions are permitted during each monthly model cycle:

- Patients in the DF state can either remain disease-free, transition to LRR, transition to DM1, or die.
- Patients in LRR can either remain in LRR, transition to DM1 or die.
- Patients in DM1 can remain in DM1, progress to DM2 or die.
- For patients in DM2, the only remaining event is death.

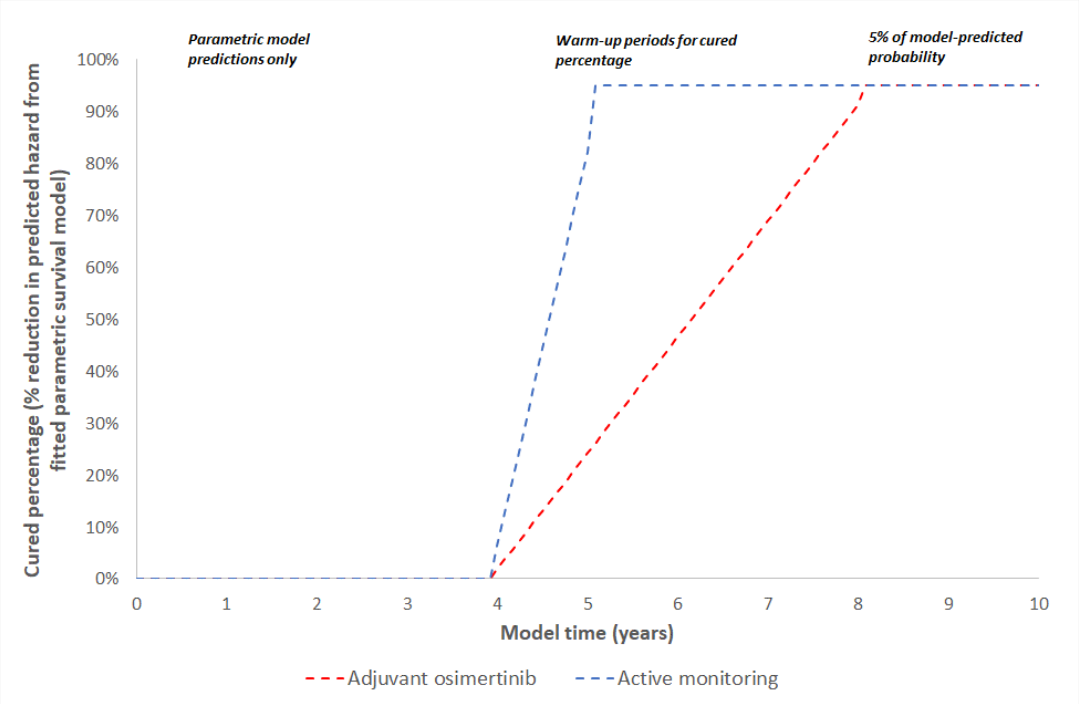
LRR, DM1 and DM2 are intermediate health states represented by sub-models which use tunnel states to allow event risks to be dependent on the time since state entry.

Transitions out of the DF state to the other alive states (Figure 10, transition probability [TP] 1 and TP2) are modelled using parametric survival models fitted to data on DFS from the ADAURA trial.[36] The transition from LRR to DM1 (Figure 10, TP4) is modelled using external data from CancerLinQ.[71] The

probability of dying in the DF and LRR states (Figure 10, TP3 and TP5) is modelled using age- and sex-matched general population life tables;[41] hence, any patient remaining in these states is assumed to have zero disease-related excess risk of death. Transitions between DM1, DM2 and dead (Figure 10, TP6, TP7 and TP8) are modelled using parametric survival models fitted to data on time to next treatment and time to death from the FLAURA RCT (osimertinib versus erlotinib/gefitinib for untreated locally advanced or metastatic EGFRm NSCLC).[39] Time to death in DM2 (TP8) is also informed by the ABCP arm of the IMPower150 trial (ABCP versus BCP for stage IV or recurrent metastatic, chemotherapy-naïve non-squamous EGFRm NSCLC).[40] The transition probabilities applied in each health state are adjusted to account for competing risks, based on an approach which is similar to that described by Putter *et al*.[72] The transitions from all alive states to the dead state include a constraint which ensures that the risk of death is at least as high as that for the age- and sex-matched general population.[41] The model includes re-calibration of some of the transition probabilities (TP4, TP6 and TP8) in both treatment groups to force the model-predicted OS function to better fit the observed OS outcomes from ADAURA.[36]

The model includes structural assumptions of cure in both treatment groups – these assumptions are implemented by reducing the risk of leaving the DF state (TP1 and TP2) at certain timepoints, including what the CS[2] refers to as a "warm-up period", as illustrated in Figure 11. In the active monitoring group, the model assumes that the probability of leaving the DF state (due to local/distant recurrence) estimated from the parametric survival models fitted to ADAURA[36] is reduced by 0% at the end of year 4, increasing approximately linearly to 95% by the end of year 5. Beyond year 5, the risk of leaving the DF state remains at 5% of the predicted probabilities obtained from the parametric survival models fitted to the placebo arm of ADAURA. A similar approach is applied in the adjuvant osimertinib group of the model, with the probability of leaving the DF state being reduced by 0% at the end of year 4, increasing approximately linearly to 95% by the end of year 8. Beyond year 8, the risk of leaving the DF state remains at 5% of the predicted probabilities obtained from the parametric survival models fitted to the adjuvant osimertinib arm of ADAURA. In both groups, these assumptions increase the probability that patients remain disease-free and thus continue to have no excess risk of NSCLC-related mortality. The cure assumptions do not apply to patients who have already developed loco-regional or distant recurrence, and patients who are disease-free are still subject to a small risk of experiencing recurrence beyond the final cure timepoint (post-cure risk=5% of predicted probabilities from the parametric survival models).

Figure 11: Illustration of the company's cure assumptions for adjuvant osimertinib and active monitoring



HRQoL is assumed to be dependent on the model health state, with higher values applied in the DF and LRR states compared with the distant metastasis states, and a higher value is applied in DM1 compared with DM2. The same utility values are applied in both treatment groups. The model also includes short-term QALY losses to reflect AEs associated with adjuvant osimertinib and active monitoring which are applied during the first model cycle only. The model does not explicitly include further QALY losses associated with AEs arising as a consequence of downstream treatments for loco-regional or distant recurrence. Health state utilities are adjusted for increasing age.[73]

The model includes costs associated with: (i) drug acquisition and administration (adjuvant treatment and downstream treatments for loco-regional and metastatic recurrences); (ii) monitoring; (iii) health state resource use; (iv) managing AEs (applied as a once-only cost); and end-of-life care. The costs of EGFR mutation testing are not included in the company's base case analysis or sensitivity analyses.

5.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- Patients with completely resected, stage IB-IIIA EGFRm NSCLC in the DF and LRR states are assumed to have no excess risk of death compared to the age- and sex-matched general population.

- Parametric survival models are used to estimate the probability of transitioning between model health states over time; the models used to estimate each set of transition probabilities are described in detail in Section 5.2.4.
- Cure is assumed in both treatment groups. In the active monitoring group, the predicted probabilities of transitioning from DF to LRR and DM1 are assumed to be reduced by 95% by the end of year 5, following a 1-year warm-up period. In the adjuvant osimertinib group, the predicted probabilities of transitioning from DF to LRR and DM1 are assumed to be reduced by 95% by the end of year 8, following a 4-year warm-up period. Unless the patient leaves the DF state, they are assumed to have zero excess risk of death, thereby assuming cure.
- All patients who enter the LRR state are assumed to receive active treatment. Similarly, all patients who enter the DM1 and DM2 states receive active therapy for metastatic disease. No patients are assumed to receive BSC alone at any treatment line.
- Eighty-three percent of patients in the active monitoring group are assumed to receive osimertinib as first-line treatment for distant metastases. The remaining 17% of patients are assumed to receive an early TKI (5% erlotinib, 3% gefitinib, 9% afatinib).
- After 4 years since initiating adjuvant treatment with osimertinib, the model assumes that 50% of patients who progress to DM1 will be re-treated with osimertinib, with the remainder receiving PDC. Prior to this timepoint, all patients who receive adjuvant osimertinib and subsequently experience distant relapse receive PDC as first-line therapy.
- Outcomes for patients receiving treatment for distant metastases are based on data from the FLAURA trial[39] and the IMPower150 trial,[40] including a calibration factor which is applied to selected transition probabilities in both treatment groups. This calibration factor adjusts modelled OS to better fit the observed OS in ADAURA.[36]
- Outcomes for patients receiving osimertinib in the metastatic setting are assumed to be independent of prior treatment with osimertinib in the adjuvant setting (i.e., re-treatment with osimertinib does not lead to any reduction in effectiveness).
- Health utility in the DF and LRR states is assumed to be equivalent and is consistently assumed to be slightly higher than that of the age- and sex-matched general population[74] in every model cycle.
- Osimertinib, early TKIs, PDC, docetaxel and ABCP are assumed to require monitoring via liver function, renal function and blood tests. All TKIs (including osimertinib) are also assumed to require additional monitoring using electrocardiograms (ECGs) and echocardiograms. Monitoring requirements for osimertinib in the adjuvant setting are assumed to be 50% of those in the metastatic setting.

- Only Grade 3/4 AEs experienced by at least two patients in ADAURA[36] are included in the model; these are assumed to impact on both QALYs and costs. AEs associated with downstream treatments for loco-regional and distant recurrence are not explicitly included.
- Health state resource use is assumed to be the same in the DM1 and DM2 states.
- CNS metastases are assumed to be experienced by 30.7% and 43.1% of patients who progress to distant metastases in the adjuvant osimertinib and active monitoring groups, based on ADAURA.[36] This event is assumed to lead to additional treatment costs.
- Vial sharing is assumed for IV chemotherapy treatment (PDC and docetaxel). Wastage is not included for any therapy in the company's base case analysis.
- Relative dose intensity (RDI) for chemotherapy treatments is assumed to be 100%. The RDI for osimertinib is assumed to be [redacted], based on data from the ADAURA trial.[36]

5.2.4 Evidence used to inform the model parameters

Table 21 summarises the evidence sources used to inform the parameters of the company's base case model; these are discussed in detail in the subsequent sections.

Table 24: Evidence used to inform the company's model

Parameter group	Source
Patient characteristics	Mean age and proportion female taken from ADAURA[36]
Transitions from DF to LRR and DM1 (TP1, TP2)	Informed by ADAURA[36]
Cure assumptions (assumed reduction in risk of relapse and associated timepoints for start and end of warm-up period)	Company's assumptions, informed by the ERG's pessimistic scenario in TA761[20] and additional input from clinical experts[7] (see clarification response,[42] questions B3 and C12)
Transition from LRR to DM1 (TP4)	Both groups: CancerLinQ[71]
Transitions between DM1 to DM2 (TP6)	Informed by FLAURA.[39] Effect of chemotherapy estimated using HR for TKI versus chemotherapy from Holleman *et al.*[75]
Transitions from DM1 to Dead (TP7) and DM2 to Dead (TP8)	TP7 informed by FLAURA[39] TP8 informed by FLAURA[39] and ABCP arm of IMPower150[39]
Transitions from DF and LRR to dead (TP3, TP5)	ONS life tables[41]
Re-treatment probability	Company's assumption, based on company's previous assumption applied in TA761 (see clarification response,[42] question C15).
Health state utility values	DF and LRR: SF-36 data from ADAURA mapped to EQ-5D-3L.[36, 52] DM1: EORTC QLQ-C30 data from FLAURA mapped to EQ-5D-3L.[39, 76] DM2 : Labbé *et al.*[69] AE disutilities: Nafees *et al.*[77] and TA653.[78]
Osimertinib acquisition costs	PAS discount for adjuvant osimertinib provided by the company.[2] Total osimertinib acquisition costs modelled using empirical TTD function from ADAURA[36] (maximum duration = 3 years).
Acquisition costs of early TKI (erlotinib, gefitinib, afatinib), PDC/ docetaxel (including pre-medication), ABCP	BNF[38] and eMIT[79]
Radiotherapy cost per fraction (for LRR)	NHS Reference Costs 2021/22[80]
RDI	Osimertinib: ADAURA[36] and FLAURA;[39] RDI for PDC and docetaxel assumed to be 100%.
Drug administration and monitoring costs	PSSRU,[81] eMIT[79] and NHS Reference Costs 2021/22.[80] Monitoring requirements for osimertinib based on TA761[20] and clinical input.[7]
Health state management costs (DF, LRR, DM1 and DM2)	Andreas *et al.*[19] with additional assumptions. Unit costs taken from NHS Reference Costs 2021/22[80]
CNS metastases management and radiotherapy (for DM1/DM2)	Reference Costs 2021/22;[80] PSSRU;[81] NICE TA536[82] and Royal College of Radiologists report[80]
Costs of managing AEs (adjuvant setting only)	Frequency of AEs taken from ADAURA.[36] Unit costs taken from NHS Reference Costs 2021/22[80]
Terminal care costs	Brown *et al.*,[70] NHS Reference Costs 2021/22,[80] PSSRU[81] and Marie Curie report[83]

ERG - Evidence Review Group; TP - transition probability; DF - disease-free; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; NSCLC - non-small cell lung cancer; RDI - relative dose intensity; TKI - tyrosine kinase inhibitor; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel; PDC - pemetrexed plus cisplatin; TTD - time to treatment discontinuation; EQ-5D-3L - Euroqol 5-Dimensions (3-level); SF-36 - Short Form 36 Items; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer quality of life questionnaire; AE - adverse event; BNF - British National Formulary; eMIT - electronic Market Information Tool; PSSRU - Personal Social Services Research Unit; CS - company's submission; PAS - Patient Access Scheme; NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal

5.2.4.1 Patient characteristics

Patient characteristics are based on the overall population of the ADAURA trial.[36] At model entry, patients are assumed to have a mean age of 63 years and 70% of patients are assumed to be female. These characteristics are used to estimate general population mortality risks and to adjust utility values for increasing age.

5.2.4.2 Transition probabilities

Summary of transitions and data sources

The company's economic model includes 22 sets of transition probabilities, including eight sets of transition probabilities for each treatment group (Figure 10, TP1 to TP8), a further three sets of transition probabilities for patients who receive adjuvant osimertinib and who are re-treated with osimertinib or treated with PDC after 4 years (rather than all receiving PDC) in the metastatic setting (Figure 10, TP6-TP8 re-treatment), and another three sets of transition probabilities for patients in the active monitoring group who experience distant relapse and receive an early TKI (rather than osimertinib) as first-line therapy (Figure 10, TP6-TP8 early TKI).

The transition probabilities for patients who leave the DF state and survive (TP1 and TP2) were estimated using parametric survival models fitted to time-to-event data from ADAURA for each treatment group[36] (DFS DCO 11th April 2022; OS DCO 27th January 2023). Owing to immaturity of the OS data from this source, external data were required to estimate all other transition probabilities. The company obtained data from the CancerLinQ database,[71] the FLAURA trial,[39] and the IMPower150 trial[40] to inform the majority of the other transition probabilities (TP4, TP6, TP7 and TP8). General population life tables for the UK[41] were used to inform transitions from DF and LRR to dead (TP3 and TP5, respectively).

CancerLinQ[71] is a real-world database which collects electronic health record data from US cancer patients. A retrospective analysis of data from CancerLinQ from the 1st January 2014 to the 31st December 2018 was conducted by the company. An "ADAURA-like" population, which was matched for baseline characteristics, was drawn from patients in the database who had EGFRm NSCLC in stage IB–IIIA following tumour resection and who had experienced loco-regional recurrence (N=97). For each patient, the time from loco-regional recurrence to distant metastases was determined, with the latter defined as the time to metastatic disease when a metastases diagnosis was found, or the date of first systemic treatment in the absence of metastatic identification.

FLAURA (NCT02296125)[39] is a completed Phase III, double-blind RCT which assessed the efficacy and safety of osimertinib versus standard of care EGFR-TKI (gefitinib or erlotinib), as first-line treatment in patients with locally advanced or metastatic EGFRm NSCLC (stage IIIB or IV) that is not

amenable to curative surgery or radiotherapy. This study formed the basis of NICE TA654 (osimertinib for untreated EGFRm NSCLC).[21] The data used in the economic model reflect the final DCO of the 25th June 2019. These data have not been updated since TA761.[20]

IMPower150[40] is completed Phase III, randomised, open-label study which assessed the efficacy of ABCP versus bevacizumab, carboplatin and paclitaxel (BCP) in chemotherapy-naïve patients with non-squamous NSCLC. The data used in the company's model relate specifically to the subgroup of patients with EGFRm NSCLC.

Section B.3.3.1 of the CS[2] states that six clinicians consulted by the company in 2020 (prior to TA761) and five clinicians interviewed by the company in 2023 were satisfied that the data from ADAURA[36] are generalisable to UK practice and that the data from CancerLinQ[71] and FLAURA[39] are appropriate and generalisable to the target population. Contradictorily, Section B.3.3.4 of the CS explains that FLAURA enrolled stage IIIB/IV newly diagnosed metastatic patients who are *"distinctly different from ADAURA patients who have received radical treatment and progressed to metastatic disease."* Because of this, the company has re-calibrated some of the post-relapse transition probabilities used in the model to better align model-predicted OS with the observed OS in ADAURA.

A range of parametric survival models were fitted to the available time-to-event data, as summarised in Table 25. Whilst the company assessed the proportional hazards (PH) assumption for pairs of treatments within ADAURA[36] and FLAURA,[39] parametric survival models were fitted separately to the data for each arm of the trials. The company used survival analysis techniques to derive event-specific hazards which, in turn, were used to derive transition probabilities to populate the company's economic model.

Several of the fitted parametric survival models were subsequently adjusted in the economic model to reflect different treatments (PDC is modelled by applying an HR of 1/0.43 for gefitinib versus chemotherapy from a published network meta-analysis [NMA][75] to the early TKI arm of FLAURA to provide survival estimates for PDC), and/or different populations (TP4, TP6 and TP8 are adjusted using a calibration factor of [redacted] with the intention of accounting for differences in outcomes between newly diagnosed stage IIIB/IV patients in FLAURA[39] and patients with metastatic relapse in ADAURA[36]). These adjustments are indicated in the footnotes to Table 25 and in the subsequent text description.

Table 25: Summary of parametric survival models used to populate the transition probabilities in the company's economic model

Dataset	Trial arm	N Patients	Event	N Events	Competing events censored	Parametric model selected	Transition(s) used in model treatment group
ADAURA[36] (overall population)	Osimertinib	339	LRR	41	DM1, death	Log-normal	TP1 Osi: DF to LRR*
	Placebo	343	LRR	76	DM1, death	Log-normal	TP1 AM: DF to LRR*
	Osimertinib	339	DM1	50	LRR, death	Log-logistic	TP2 Osi :DF to DM1*
	Placebo	343	DM1	124	LRR, death	Log-normal	TP2 AM: DF to DM1*
CancerLinQ[71]	N/a	97	DM1	54	Death	Log-normal	TP4 both groups: LR to DM1¶
FLAURA[39]	Osimertinib	279	DM2	100	Death	Weibull	TP6 Osi (osi re-treated): DM1 to DM2 (represents 50% of the retreated group who are re-treated with osimertinib after 4 years)¶ TP6 AM (osi treated): DM1 to DM2¶
	Erlotinib/ gefitinib	277	DM2	116	Death	Weibull	TP6 Osi (osi re-treated): DM1 to DM2 (represents 50% of the retreated group who are treated with PDC after 4 years)† TP6 Osi (not re-treated): DM1 to DM2† TP6 AM (TKI treated): DM1 to DM2¶
	Pooled arms	556	Death	11	TTD (DM2 proxy)	Exponential	TP7 both groups: DM1 to Dead
	Osimertinib post-TTD	205	Death	148	N/a	Weibull	TP8 Osi (osi re-treated): DM2 to Dead‡¶ TP8 AM (osi treated): DM2 to Dead‡¶
	Erlotinib/gefitinib post-TTD	259	Death	149	N/a	Weibull	TP8 Osi (not re-treated): DM2 to Dead¶ TP8 AM (TKI treated): DM2 to Dead‡¶
IMPower150[40]	ABCP arm	34	Death	23	N/a	Weibull	TP8 Osi: DM2 to Dead§ TP8 AM: DM2 to Dead§
General population life tables[41]	N/a	N/a	Death	N/a	N/a	N/a	TP3 both groups: DF to Dead TP5 both groups: LRR to Dead

N - number; TP - transition probability; Osi - osimertinib; AM - active monitoring; DF - disease-free; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; TTD - time to treatment discontinuation; PDC - pemetrexed and cisplatin; TKI - tyrosine kinase inhibitor; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel; N/a - not applicable; NR - not reported

** The company's model applies structural cure assumptions to these transitions whereby 95% of patients are assumed cured by 5 years in the active monitoring group and 8 years in the adjuvant osimertinib group, with a warm-up period in both treatment groups starting after 4 years.*

†Outcomes for the early TKI arm in FLAURA are adjusted using a hazard ratio of 1/0.43 from Holleman et al.[75] to reflect outcomes for chemotherapy in the company's economic model.

‡TKI arm or osimertinib arm in FLAURA represents 80% of weighted survival model for TP8.

§ABCP arm of the IMPower150 represents 20% of weighted survival model for TP8.

¶These transition probabilities are adjusted using a calibration factor of [redacted].

Summary of survival modelling methods

For each transition, the company fitted six standard parametric survival models to the available data. These included the exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma survival distributions. The 2-parameter gamma and generalised F distributions were not considered in the analysis. Mixture-cure models (MCMs) and restricted cubic spline (RCS) models were not considered.

The company's survival analysis includes adjustments to account for competing risks. For each transition which is subject to competing events, for example, the transition from DF to LRR (TP1), the available time-to-event data were processed to include only the event of interest (loco-regional recurrence), with the competing event(s) not of interest (distant recurrence and death) treated as censored observations. Parametric survival models were then fitted to these data, as described below. The company's economic model then adjusts for competing risks by multiplying the cause-specific event hazard (e.g., the risk of LRR) by the joint probability of experiencing any event (loco-regional recurrence, distant recurrence or death). The EAG notes that all plots of cumulative survival probabilities for individual events presented in this section include censoring for the event not of interest. As such, care should be taken to avoid misinterpreting the Kaplan-Meier survival functions used in the analysis, as the censoring of the competing risks results in an upward bias on survival probabilities. However, this does not compromise the use of the parametric survival models to estimate the hazards in each case.

The company's approach to parametric model selection included consideration of several factors: (i) visual fit of the fitted models to the Kaplan-Meier plots; (ii) statistical goodness-of-fit based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), (iii) the empirical and modelled hazard functions (TP1 and TP2 only) and (iv) the clinical plausibility of survival extrapolations, including reference to external clinical data and expected background mortality. The company's model selection process is detailed below for each individual transition. However, one of the key criteria used for TP1 and TP2 in both treatment groups was whether the parametric survival model predictions were consistent with an assumption of cure. The EAG also notes that whilst the company's parametric survival model selection process included consideration of statistical goodness-of-fit using AIC and BIC, the CS[2] cites a paper on multistate modelling by Williams *et al*.[84] which explains that AIC is not an appropriate measure in a competing risks setting. As such, the estimates of statistical goodness-of-fit presented by the company may not be meaningful for most of the transitions.

Cure assumption

As described in Section 5.2.2, the company's model includes a cure assumption whereby the predicted probabilities of leaving the DF state are assumed to be reduced by 95% after 5 years in the active

monitoring group and after 8 years in the osimertinib-treated group, with a preceding warm-up period in each treatment group starting after 4 years. During this warm-up period, the cured proportion, which is implemented as a proportionate reduction in the predicted probability of relapse from the fitted survival models, increases approximately linearly during each monthly cycle (see Figure 11). Patients remaining in the DF health state beyond the cure timepoint are assumed to have the same mortality risk as the general population. This should be borne in mind when interpreting the company's survival analyses for transitions leaving the DF health state based on ADAURA[36] (TP1 and TP2). The plots of model-predicted probabilities of experiencing distant relapse and loco-regional recurrence, as shown in Figure 13, Figure 14, Figure 16 and

Figure 17, reflect the fitted parametric survival model predictions and do not show the impact of the company's additional structural cure assumptions.

The company's cure assumptions were informed by advice provided by six UK clinicians in a survey undertaken by the company in 2020 (prior to TA761),[85] and by a series of one-to-one interviews between the company and five UK clinicians in 2023.[7] The clinicians supported the following assertions:

- Patients are at greatest risk of recurrence between 18 and 24 months following surgical resection.
- Patients are typically discharged at 5 years if no recurrence has occurred and can be considered functionally cured.
- Patients are functionally cured if they had not experience disease recurrence 5 years after completing treatment with adjuvant osimertinib (by 8 years after starting treatment).
- It can be reasonably assumed that survival will subsequently be similar to that of the general population.
- The significant DFS benefit with osimertinib observed in ADAURA[36] (see Section 4.2) will translate into a greater proportion of osimertinib-treated patients achieving cure, compared with placebo (active monitoring).

Further support for the inclusion of a cure assumption was drawn from the ADAURA trial[36] in that, compared with the control group, the adjuvant osimertinib group had a higher proportion of recurrences which were loco-regional rather than distant. There was also a significant reduction of risk of CNS

recurrence or death with osimertinib in the overall trial population. In addition, the company fitted MCMs to data on DFS from the ANITA trial[86] (adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA), which suggested curative potential for a proportion of patients, albeit in a separate study to ADAURA (estimated cure fractions ranged from 16% to 31%; further details are provided in Section B.3.3.3.1 of the CS[2]).

TP1: Disease-free to loco-regional recurrence

The transitions from DF to LRR (TP1) were based on data for the time to loco-regional recurrence from ADAURA[36] with competing events (distant recurrence and death) censored. The six candidate survival distributions were fitted separately to the data for each treatment group in ADAURA. AIC and BIC statistics for the fitted parametric survival models for the adjuvant osimertinib and placebo groups are presented in Table 26 and Table 27, respectively. Empirical (smoothed) and modelled hazard plots for both treatment groups are presented in Figure 12. The Kaplan-Meier survival functions and the parametric survival model predictions for the adjuvant osimertinib and placebo groups are shown in Figure 13 and Figure 14, respectively.

The CS[2] indicates that consideration of goodness-of-fit, the hazard functions and clinical plausibility (including an expectation of cure by 5 years for active monitoring and by 8 years for adjuvant osimertinib), were used as criteria for selecting the preferred survival functions for TP1.

Amongst the six fitted parametric survival models, the log-normal distribution had the lowest AIC in the osimertinib group and the lowest BIC in both treatment groups. The generalised gamma distribution had the lowest AIC in the placebo group. The CS[2] notes that the hazard function for the generalised gamma model deviates from the empirical hazard functions in both groups. In terms of clinical plausibility, the CS[2] states that given the expectation of a plateau and functional cure by 8 years in osimertinib-treated patients, the Gompertz, Weibull and log-logistic distributions were excluded because they were *"too pessimistic and clinically implausible."* With respect to the placebo group, in which an assumption of cure is expected by 5 years, all parametric models except for the Gompertz distribution were considered to be potentially clinically plausible. Based on the AIC/BIC statistics, the hazard plots and the plausibility of the fitted models, the company selected the log-normal distribution for both treatment groups in the base case analysis. The company undertook scenario analyses using the Weibull distribution for the osimertinib group and the generalised gamma distribution for the active monitoring group (see Table 47).

Table 26: AIC and BIC statistics, DF to LRR (TP1), ADAURA, osimertinib group

Distribution	AIC	BIC
Exponential*	572.92	576.75
Weibull	568.98	576.63
Gompertz	570.55	578.2
Log-normal (base case)*	**567.87**	**575.51**
Log-logistic	569	576.66
Generalised gamma*	569.63	581.11

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible by the company.

Table 27: AIC and BIC statistics, DF to LRR (TP1), ADAURA, placebo group

Distribution	AIC	BIC
Exponential*	913.12	916.96
Weibull*	914.82	922.49
Gompertz	910.29	917.96
Log-normal (base case)*	905.73	**913.40**
Log-logistic*	911.67	919.34
Generalised gamma*	**903.18**	914.69

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible by the company.

Figure 12: Empirical (smoothed) and modelled hazard functions, DF to LRR (TP1), ADAURA, osimertinib and placebo groups (reproduced from CS, Figure 25)

Note: The dashed black line represents the smoothed empirical hazard

Figure 13: Observed Kaplan-Meier plot and modelled survival distributions, DF to LRR (TP1), ADAURA, osimertinib group

KM - Kaplan-Meier

Figure 14: Observed Kaplan-Meier plot and modelled survival distributions, DF to LRR (TP1), ADAURA, placebo group

KM - Kaplan-Meier

TP2: Disease-free to first-line treatment for distant metastases

The transitions from DF to DM1 (TP2) were informed by data on the time to distant metastases from ADAURA[36] with competing events (loco-regional recurrence and death) censored. AIC and BIC statistics for the fitted models for the adjuvant osimertinib and placebo groups are presented in Table 28 and Table 29, respectively. Empirical (smoothed) and modelled hazard plots for both treatment groups are presented in Figure 15. The Kaplan-Meier survival functions and the parametric survival model predictions for the adjuvant osimertinib and placebo groups are shown in Figure 16 and Figure 17, respectively.

Amongst the six fitted parametric survival models, the log-logistic distribution had the lowest AIC and BIC in the osimertinib group, whereas the generalised gamma distribution had the lowest AIC and BIC in the placebo group. The Weibull distribution provided a similar fit in the osimertinib group. The CS[2] highlights discrepancies between the empirical and modelled hazards for the generalised gamma distribution in the placebo group, and for the log-normal distribution in the osimertinib group. The CS states that for the adjuvant osimertinib group, the exponential distribution was ruled out due to poor visual fit, and the Gompertz and Weibull distributions were ruled out as they were inconsistent with expectations of cure by 8 years and were therefore clinically implausible. For the placebo group, whereby the company states that cure is expected by 5 years, all parametric models were considered to be potentially clinically plausible. Based on AIC/BIC statistics, the hazard plots and the plausibility of the fitted models, the company selected the log-logistic distribution for the adjuvant osimertinib group and the log-normal distribution for the placebo group. The company undertook scenario analyses using the log-normal distribution for the adjuvant osimertinib group and the generalised gamma distribution for the placebo group (see Table 47).

Table 28: AIC and BIC statistics, DF to DM1 (TP2), ADAURA, osimertinib group

Distribution	AIC	BIC
Exponential	675.46	679.29
Weibull	630.62	638.27
Gompertz	636.02	643.67
Log-normal*	631.33	638.98
Log-logistic (base case)*	**630.35**	**638.01**
Generalised gamma*	632.37	643.84

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible by the company.
Note: This table contains corrected values provided by the company following the clarification round.

Table 29: AIC and BIC statistics, DF to DM1 (TP2), ADAURA, placebo group

Distribution	AIC	BIC
Exponential*	1,361.67	1,365.51
Weibull*	1,362.21	1,369.88
Gompertz*	1,353.08	1,360.76
Log-normal (base case)*	1,344.13	1,351.80
Log-logistic*	1,354.22	1,361.90
Generalised gamma*	**1,335.81**	**1,347.32**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible by the company.

Figure 15: Empirical (smoothed) and modelled hazard functions, DF to DM1 (TP2), ADAURA, osimertinib and placebo groups (reproduced from CS, Figure 31)

Note: The dashed black line represents the smoothed empirical hazard

Figure 16: Observed Kaplan-Meier plot and modelled survival distributions, DF to DM1 (TP2) ADAURA, osimertinib group

KM - Kaplan-Meier

Figure 17: Observed Kaplan-Meier plot and modelled survival distributions, DF to DM1 (TP2), ADAURA, placebo group

KM - Kaplan-Meier

TP3: Disease-free to Dead

At the April 2022 DCO, there were very few deaths amongst those patients without relapse in ADAURA[36] (N=7). As such, the transition from DF to dead was instead modelled using age- and sex-matched UK general population life tables.[41] Therefore, the model assumes that patients who do not relapse have no excess risk of mortality compared to the general population.

TP4: Loco-regional recurrence to first-line treatment for distant metastases

Owing to the immaturity of the ADAURA trial data,[36] the company was unable to use this source to estimate transition rates from LRR to DM1. Instead, data from CancerLinQ[71] on time from loco-regional recurrence to metastatic disease when a metastases diagnosis was found or the date of first systemic treatment in the absence of metastatic disease identification were used to estimate the rate of transition from LRR to DM1, assuming the same risk in both the adjuvant osimertinib and active monitoring groups. The EAG assumes that the competing event of death was censored when processing these data, although this is not explicitly stated in the CS.[2] The six candidate survival distributions were fitted to the available individual patient data (IPD). AIC and BIC statistics for the fitted models are

presented in Table 30. Empirical and modelled hazard plots are not presented in the CS for this endpoint; following a request from the EAG, these plots were included as part of the company's clarification response[42] (question C3, see Figure 18). The Kaplan-Meier function and the parametric survival model predictions for this event are shown in Figure 19.

Amongst the six fitted parametric survival models, the generalised gamma distribution had the lowest AIC and BIC. The company ruled out the exponential and Weibull distributions because they were considered overly pessimistic, whereas the Gompertz and generalised gamma distributions were ruled out because they were considered overly optimistic. The CS[2] highlights that the log-normal and log-logistic distributions provide a very similar visual fit to the observed data. The log-normal distribution was selected for inclusion in the company's base case due to its better statistical fit as judged by AIC and BIC. Hazard plots were not used to inform model selection for this endpoint. No alternative survival distributions for TP4 were considered in the company's scenario analyses.

Table 30: AIC and BIC statistics, LRR to DM1 (TP4), CancerLinQ, applied to both treatment groups

Distribution	AIC	BIC
Exponential	447.83	450.40
Weibull	436.34	441.49
Gompertz	432.72	437.87
Log-normal (base case)*	427.52	432.67
Log-logistic*	431.48	436.63
Generalised gamma	**422.30**	**430.03**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible by the company.

Figure 18: Empirical (smoothed) and modelled hazard functions, LRR to DM1 (TP4), CancerLinQ, both treatment groups (reproduced from clarification response, Figure 3)

[redacted]

Figure 19: Observed Kaplan-Meier plot and modelled survival distributions, LRR to DM1 (TP4) for both groups, CancerLinQ

KM - Kaplan-Meier

TP5: Loco-regional recurrence to dead

Owing to the immaturity of the data and the lack of relevant events in ADAURA,[36] and the small number of deaths observed the CancerLinQ dataset[71] (N=2), the transition from loco-regional recurrence to dead was based on UK general population life tables.[41] The hazard of this event is therefore the same as that used for TP3 (DF to death). The CS[2] (page 107) comments that the risk of death from LRR is higher than that from DF due to the higher risk of reaching the death state via DM1. The EAG agrees, but notes that given the structure of the company's model, the per-cycle mortality risk is determined by the patient's current health state.

TP6: First-line treatment for distant metastases to second-line treatment for distant metastases

The company's economic model applies includes four different sets of transition probabilities for TP6 - two in each modelled treatment group. Each of these sets of transition probabilities were estimated using parametric survival models fitted to data on TTD (censored for death) from FLAURA:[39]

- TP6(a) - Adjuvant osimertinib group, patients who are not re-treated with osimertinib in DM1: Based on a parametric survival model fitted to the erlotinib/gefitinib arm of FLAURA[39] and

adjusted using an HR for TKI versus chemotherapy from Holleman *et al.*[75] This function is used only during the first 4 years of the model time horizon (prior to the re-treatment timepoint).

- TP6(b) - Adjuvant osimertinib group, patients who are re-treated with osimertinib in DM1: Estimated as a weighted survival model comprising 50% of a survival model fitted to the osimertinib arm in FLAURA[39] and 50% of a survival model fitted to the erlotinib/gefitinib arm in FLAURA. Survival in the latter group is again adjusted using the HR for TKI versus chemotherapy from Holleman *et al.*[75] This weighted survival function is applied to all patients in the adjuvant osimertinib group who reach the DM1 health state after the first 4 years of the model time horizon (after the re-treatment timepoint).
- TP6(c) - Active monitoring group, patients who receive osimertinib in DM1: Estimated using a parametric survival model fitted to the osimertinib arm of FLAURA.[39]
- TP6(d) - Active monitoring group, patients who receive an early TKI in DM1: Estimated using a parametric survival model fitted to the erlotinib/gefitinib arm of FLAURA.[39]

Some of these transition probabilities are then further adjusted by the company's calibration factor (the part of TP6(b) which relates to the FLAURA erlotinib/gefitinib arm, and all of TP6(c) and TP6(d)).

The CS[2] states that data on TTD (censoring for deaths) were used instead of progression-free survival (PFS) for this transition because PFS was only collected up to DCO1 in FLAURA[39] (June 2017), whereas TTD and OS were collected up to DCO2 (June 2019). The six candidate survival distributions were fitted to the available data from FLAURA for each arm. AIC and BIC statistics for the models fitted to the osimertinib and erlotinib/gefitinib groups of FLAURA are presented in Table 31 and Table 32, respectively. Empirical and modelled hazard plots for this event are not presented in the CS,[2] but were provided later as part of the company's clarification response[42] (see Figure 20 and Figure 21). The Kaplan-Meier survival functions and the parametric survival model predictions for the osimertinib and erlotinib/gefitinib groups of FLAURA[39] are shown in Figure 22 and Figure 23, respectively. These plots do not include the subsequent adjustment using the HR from Holleman *et al.*,[75] or any subsequent re-calibration.

Amongst the six fitted parametric survival models fitted to the data for the osimertinib group of FLAURA,[39] the Weibull distribution had lowest AIC and the exponential distribution had the lowest BIC. Within the erlotinib/gefitinib group, the Weibull distribution had the lowest AIC and BIC. The hazard plots were not used to inform parametric survival model selection for this endpoint. The company ruled out the log-normal and log-logistic distributions for both treatment groups because they suggested implausibly high TTD in the tails. The four remaining survival distributions were considered to be very similar. The company selected the Weibull distribution for both arms in the base case analysis

because it was stated to have the best statistical fit based on the AIC and BIC values (see Table 32). No alternative survival distributions for TP6 were considered in the company's scenario analyses.

Table 31: AIC and BIC statistics, DM1 to DM2 (TP6), FLAURA, osimertinib arm

Distribution	AIC	BIC
Exponential*	1867.24	**1870.87**
Weibull (base case)*	**1865.18**	1872.45
Gompertz*	1868.25	1875.51
Log-normal	1886.11	1893.37
Log-logistic	1865.74	1873.00
Generalised gamma*	1866.59	1877.48

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible by the company.

Table 32: AIC and BIC statistics, DM1 to DM2 (TP6), FLAURA, erlotinib/gefitinib arm

Distribution	AIC	BIC
Exponential*	1951.26	1954.89
Weibull (base case) *	**1945.91**	**1953.15**
Gompertz*	1950.20	1957.45
Log-normal	1999.94	2007.19
Log-logistic	1966.60	1973.85
Generalised gamma*	1947.90	1958.77

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible by the company.

Figure 20: Empirical (smoothed) and modelled hazard functions, DM1 to DM2 (TP6), FLAURA, osimertinib group (reproduced from clarification response, Figure 5)

Figure 21: Empirical (smoothed) and modelled hazard functions, DM1 to DM2 (TP6), FLAURA, erlotinib/gefitinib group (reproduced from clarification response, Figure 4)

Figure 22: Observed Kaplan-Meier plot and modelled survival distributions, DM1 to DM2 (TP6), FLAURA, osimertinib arm

KM - Kaplan-Meier

Figure 23: Observed Kaplan-Meier plot and modelled survival distributions, DM1 to DM2 (TP6), FLAURA, erlotinib/gefitinib arm

KM - Kaplan-Meier

TP7: First-line treatment for distant metastases to dead

For the transition from DM1 to dead (TP7), the same parametric survival model was used for all patients, regardless of prior or current treatment. The six candidate parametric survival models were fitted to pooled data on time to death from the osimertinib and erlotinib/gefitinib arms of FLAURA[39] (censored for treatment discontinuation). AIC and BIC statistics for the fitted models are presented Table 33. Empirical and modelled hazard plots for this event are not presented in the CS,[2] but were provided as part of the company's clarification response[42] (question C3; see Figure 24). The Kaplan-Meier functions and the parametric survival model predictions for this event are shown in Figure 25.

The generalised gamma distribution did not converge and therefore was not considered further. Amongst the five remaining models, the exponential distribution had the best statistical fit based on AIC and BIC and was the model that the company considered to be the least clinically implausible, although all parametric survival models suggested a lower mortality risk than that of the general population. The hazard plots were not used to inform model selection. No alternative survival distributions for TP7 were considered in the company's scenario analyses.

Table 33: AIC and BIC statistics, DM1 to Dead (TP7), FLAURA, both treatment groups pooled

Distribution	AIC	BIC
Exponential (base case)*	**174.97**	**179.29**
Weibull	175.94	184.58
Gompertz	175.4	184.05
Log-normal	175.38	184.03
Log-logistic	175.91	184.55
Generalised gamma	N/a	N/a

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; N/a - not applicable
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were considered to be potentially plausible (partially) by the company.

Figure 24: Empirical (smoothed) and modelled hazard functions, DM1 to Dead (TP7), FLAURA, both treatment groups (reproduced from clarification response, Figure 6)

Figure 25: Observed Kaplan-Meier plot and modelled survival distributions, DM1 to Dead (TP7), FLAURA, both treatment groups pooled

KM - Kaplan-Meier

TP8: Second-line treatment of distant metastases (DM2) to dead

The company's economic model applies includes four sets of transition probabilities for TP8 - two in each modelled treatment group. These four sets of transition probabilities were estimated using parametric survival models fitted to data on time from treatment discontinuation to death from FLAURA[39] and to data on OS from IMPower150:[40]

- TP8(a) - Adjuvant osimertinib group, patients who were not re-treated with osimertinib in DM1 prior to 48 months: Estimated using a parametric survival model fitted to the erlotinib/gefitinib arm of FLAURA,[39] adjusted using the HR for TKI versus chemotherapy from Holleman *et al.*[75] None of these patients are assumed to receive ABCP as second-line treatment.
- TP8(b) - Adjuvant osimertinib group, patients who entered the re-treatment sub-model in DM1 after 48 months: Estimated using a weighted survival model comprising 80% of a survival model fitted to the osimertinib arm of FLAURA[39] plus 20% of a survival model fitted to the ABCP arm of IMPower150.[40]
- TP8(c) - Active monitoring group, patients who received osimertinib in DM1: Same as TP8(b).
- TP8(d) - Active monitoring group, patients who received an early TKI in DM1: Estimated using a weighted survival model comprising 80% of a survival model fitted to the erlotinib/gefitinib arm of FLAURA[39] plus 20% of a survival model fitted to the ABCP arm of IMPower150.[40]

Some of these transition probabilities are further adjusted by the company's calibration factor (all of TP8(a) and the parts of TP8(b)-(d) which are based on FLAURA rather than IMPower150). There are no competing risks for this transition as the only remaining event is death.

As the company did not have access to IPD from IMPower150, pseudo-IPD were generated from Kaplan-Meier plots from the trial publication (Reck *et al.*[40]) using the algorithm reported by Guyot *et al.*[87] The six candidate survival distributions were fitted to the available IPD from FLAURA[39] and pseudo-IPD from IMPower150.[40] AIC and BIC statistics for the models fitted to the osimertinib and erlotinib/gefitinib arms of FLAURA and the ABCP arm of IMPower150 are presented in Table 34, Table 35, and Table 36, respectively. Empirical and modelled hazard plots for this endpoint are not presented in the CS,[2] but were provided in the company's clarification response[42] (question C3; see Figure 26 and Figure 27). The Kaplan-Meier survival functions and the parametric survival model predictions for the osimertinib and erlotinib/gefitinib arms of FLAURA and the ABCP arm of IMPower150 are presented in Figure 28, Figure 29 and

Figure 30, respectively. The cumulative survival estimates and AIC/BIC statistics relating to the survival models fitted to these data are not reported in the CS;[2] instead, these have been extracted from the company's model by the EAG. The Kaplan-Meier plot for the IMPower150 study is not provided in the company's model.

Amongst the six models fitted to the FLAURA data,[39] the Weibull distribution had the lowest AIC and BIC values in both treatment groups. The hazard plots were not used to inform model selection. The CS[2] states that with respect to the models fitted to the FLAURA data, the log-logistic and log-normal distributions were excluded given their poor fit to the observed data, and the Gompertz distribution was ruled out because it predicted substantial long-term survival which was deemed clinically implausible. The company selected the Weibull distribution for both arms of FLAURA because it had the best statistical fit by AIC and BIC. The reasons for ruling out of the exponential and generalised gamma distributions are not clearly described in the CS.

With respect to the ABCP arm of IMPower150,[40] the exponential distribution had the lowest AIC and BIC values. However, the CS[2] states that the Weibull distribution was selected for inclusion in the base case analysis in order to be consistent with the models fitted to the FLAURA data.[39]

No alternative survival distributions for TP8 were considered in the company's scenario analyses.

Table 34: AIC and BIC statistics, DM2 to Dead (TP8), FLAURA, osimertinib arm

Distribution	AIC	BIC
Exponential	1118.40	1121.73
Weibull (base case)*	**1106.90**	**1113.55**
Gompertz	1114.31	1120.96
Log-normal	1125.08	1131.72
Log-logistic	1117.82	1124.47
Generalised gamma*	1108.51	1118.48

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were mentioned in the CS as being potentially plausible.

Table 35: AIC and BIC statistics, DM2 to Dead (TP8), FLAURA, erlotinib/gefitinib arm

Distribution	AIC	BIC
Exponential	1329.18	1332.73
Weibull (base case)*	**1316.81**	**1323.93**
Gompertz	1323.71	1330.83
Log-normal	1324.37	1331.48
Log-logistic	1322.66	1329.78
Generalised gamma*	1318.73	1329.40

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Asterisks indicate models which were mentioned in the CS as being potentially plausible.

Table 36: AIC and BIC statistics, DM2 to Dead (TP8), IMPower150, ABCP arm (values reported in the company's economic model)

Distribution	AIC	BIC
Exponential	**100.47**	**102.00**
Weibull (base case)	102.24	105.29
Gompertz	102.47	105.52
Log-normal	101.94	104.99
Log-logistic	101.99	105.05
Generalised gamma	103.93	108.51

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion
AIC/BIC for best-fitting model highlighted in bold. Potentially plausible models are not discussed in the CS.

Figure 26: Empirical (smoothed) and modelled hazard functions, DM2 to Dead (TP8), FLAURA, osimertinib group (reproduced from clarification response, Figure 8)

Figure 27: Empirical (smoothed) and modelled hazard functions, DM2 to Dead (TP8), FLAURA, erlotinib/gefitinib group (reproduced from clarification response, Figure 7)

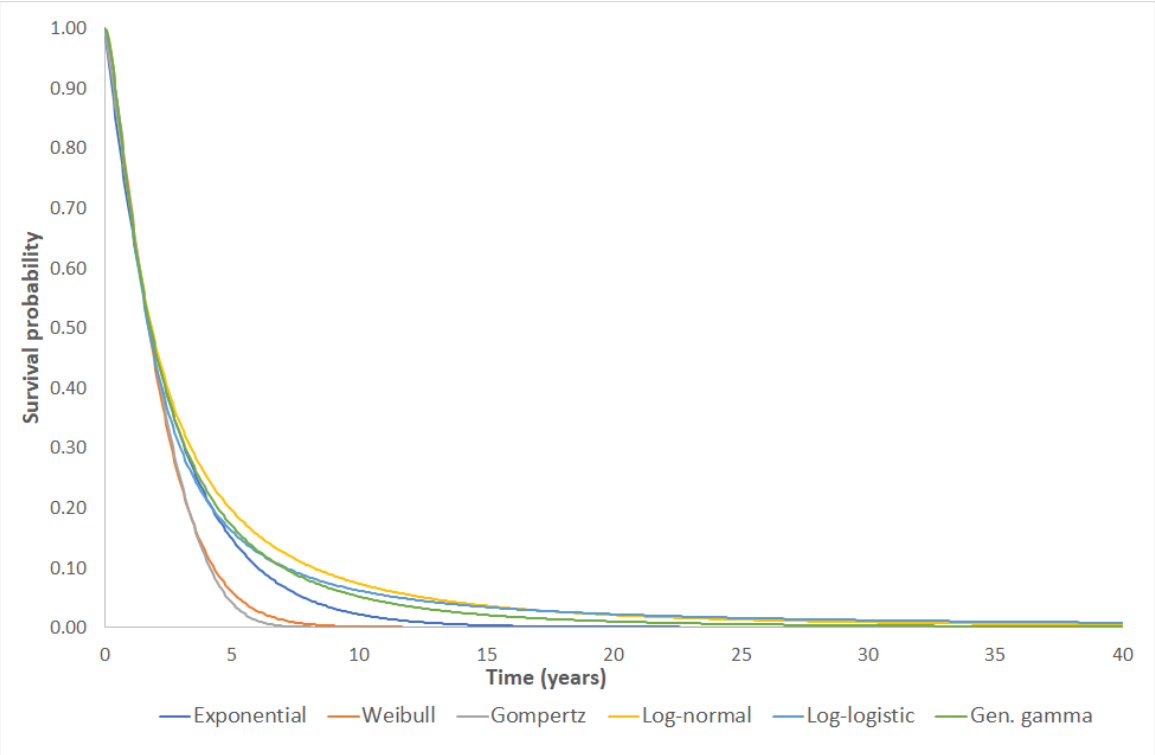
Figure 28: Observed Kaplan-Meier plot and modelled survival distributions, DM2 to Dead (TP8), osimertinib, FLAURA

KM - Kaplan-Meier

Figure 29: Observed Kaplan-Meier plot and modelled survival distributions, DM2 to Dead (TP8), erlotinib/gefitinib, FLAURA

KM - Kaplan-Meier
Note: The company's model includes an error whereby the survival model coefficients for the Gompertz, log-normal, log-logistic and generalised gamma distributions in TP8 are the same for both osimertinib and erlotinib/gefitinib. This error is reproduced in the plot above.

Figure 30: Modelled survival distributions, DM2 to Dead (TP8), ABCP, IMPower150

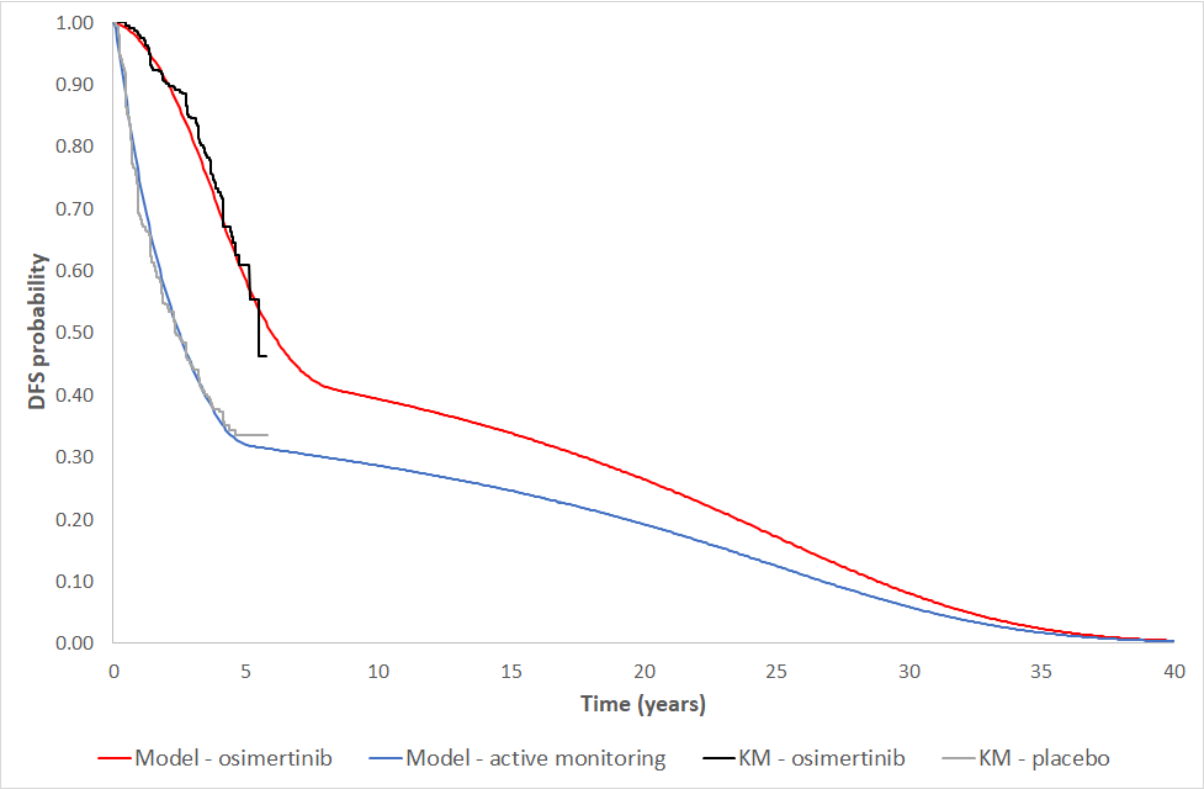


Note: The Kaplan-Meier plot for the IMPower150 data used for model fitting is not included in the company's executable model. The EAG digitised data for the EGFR subgroup of the ABCP arm of IMPower150 (Reck et al.[40]). The parametric models did not appear to fit these data well.

Model-predicted aggregate DFS

Within the company's economic model, DFS is modelled as a function of TP1, TP2 and TP3, based on the parametric survival models and cure assumptions described above. The Kaplan-Meier function for DFS in ADAURA[36] and the aggregated DFS predictions generated by the company's economic model are shown Figure 31.

Figure 31: Observed Kaplan-Meier DFS plot from ADAURA and company's aggregated DFS model predictions, including the impact of structural cure assumptions



DFS - disease-free survival; KM - Kaplan-Meier

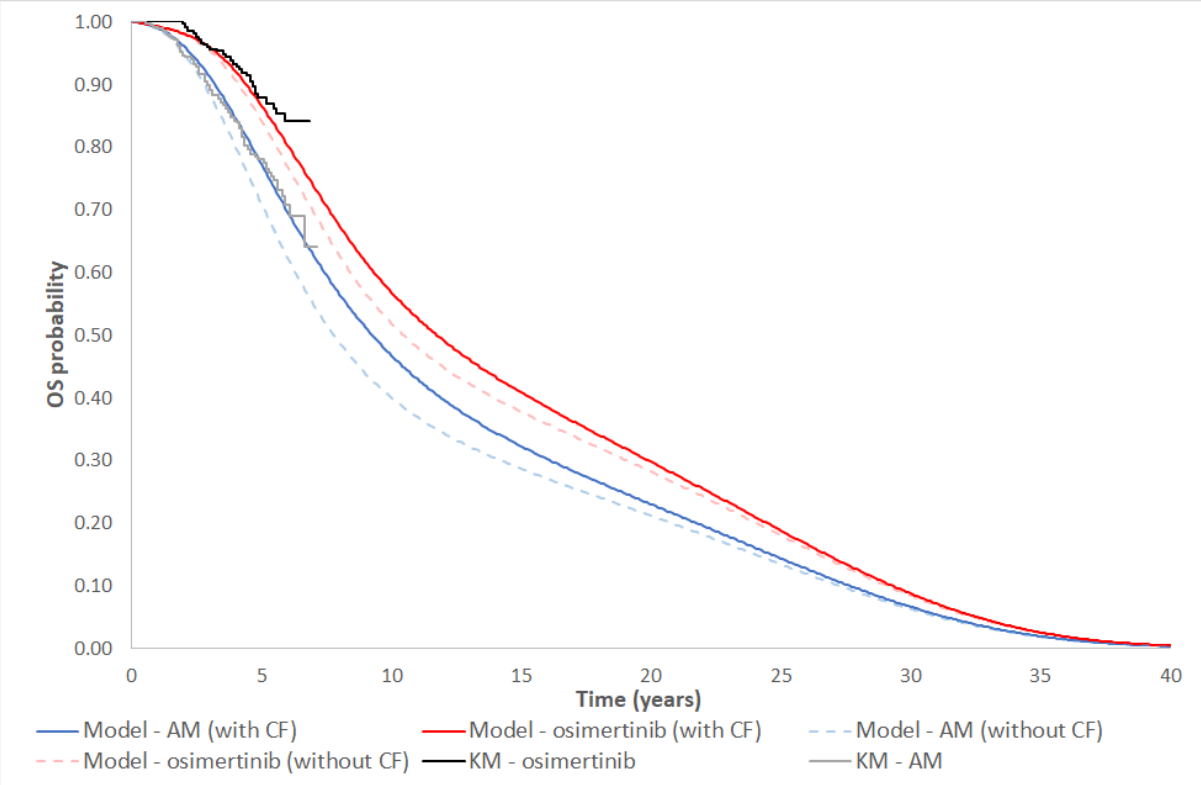
Model-predicted aggregate OS including re-calibration

Within the company's economic model, OS is modelled as a function of all of the transition probabilities (TP1-TP8), assumptions regarding how many patients follow each treatment sequence, the HR from Holleman *et al.*,[75] and an additional calibration factor which is applied to three of the sets of transition probabilities in each treatment group (TP4, TP6 and TP8).

Section 3.3.4 of the CS[2] states that ADAURA[36] is comprised of patients who progressed to distant metastases after radical treatment (surgery), whereas the population in FLAURA[39] reflects newly diagnosed patients with distant metastases who have a comparatively worse prognosis than relapsed patients under active monitoring. In order to adjust for the differences in expected outcomes between the two patient populations, the company applied a calibration factor to some transition probabilities which influence post-relapse survival (TP4, TP6 and TP8) to minimise the differences between the ADAURA Kaplan-Meier OS function and model-predicted OS. The calibration factor was calculated by minimising the sum of absolute differences in the area under the curves between the observed and model-predicted OS for both the adjuvant osimertinib and active monitoring groups. The same calibration factor of [redacted] is applied to all calibrated transition probabilities in the model. Figure 32 presents the observed Kaplan-Meier function for OS from ADAURA together with the aggregated OS

predictions generated using the company's economic model (note - the solid lines in the plot include the impact of the calibration factor, whereas the dashed lines exclude this adjustment).

Figure 32: Observed Kaplan-Meier OS plot from ADAURA and company's aggregated OS model predictions, including the impact of structural cure assumptions, with and without the calibration factor



OS - overall survival; KM - Kaplan-Meier; CF - calibration factor; AM - active monitoring

5.2.4.3 Health-related quality of life

Health state utility values applied in the DF and LRR states of the model are based on HRQoL data from the ADAURA trial,[36] whereas utility values for the DM1 and DM2 states were based on FLAURA[39] and Labbé *et al*.[69] These are described in further detail below.

Health utility values applied in the DF and LRR health states

As described in Section 4.2.6.3, ADAURA[36] included the collection of HRQoL data using the SF-36 instrument. Assessments were undertaken at baseline, day 1 (pre-dose), 12 weeks, 24 weeks and then every additional 24 weeks from randomisation (±7 days) until treatment completion (3 years) or discontinuation.[2] HRQoL data were not collected following disease relapse. The company mapped the available SF-36 data onto the EQ-5D-3L using a random effects generalised least squares (GLS) model reported by Rowen *et al*.[52] The selected regression model includes main effects, squared terms and interaction terms for the SF-36 dimensions and was estimated using prospective survey data from the Health Outcomes Data Repository (HODaR).[88] Observations with missing data from ADAURA were

excluded although the CS[2] notes that [redacted] The mapped data from ADAURA are summarised in Figure 33. As shown in the figure, the mapped EQ-5D-3L utility values were generally high (utility ≥[redacted]) at all timepoints and were similar between the two treatment groups, with a general trend for improved utility in the placebo group. The company's clarification response[42] (question C30) states that the HRQoL data from ADAURA have not been updated since TA761 as sufficient data were available from the earlier DCO.

Figure 33: Mean EQ-5D-3L in ADAURA - all observations (reproduced from CS, Figure 46)

[redacted]

The company applied repeated measures mixed effect (RMME) models to the mapped EQ-5D-3L data including three covariates: (i) Grade ≥3 AEs; (ii) baseline utility; and (iii) treatment group. The company's preferred RMME model included 337 patients in the osimertinib group and 341 patients in the placebo group of ADAURA.[2] The company used a backwards step-wise approach to remove non-significant predictors from the final RMME model, using a *p*-value threshold of 0.05. Selection of the final model was based on consideration of the AIC and BIC statistics. Treatment group was found to be non-significant; hence, this covariate and related interaction terms were excluded from the final model. The parameters of the final RMME model are summarised in Table 37. The model predicts a mean utility excluding AEs of 0.825. This utility value is applied in both the DF and LRR states of the company's base case model.

Table 37: Final RMME model applied in company's base case (adapted from CS, Table 36)

Model term	Estimate	SD
Intercept	[redacted]	[redacted]
Covariate 1 (AE)	[redacted]	[redacted]
Covariate 2 (Baseline)	[redacted]	[redacted]

SD - standard deviation; AE - adverse event

Health utility values applied in the DM1 and DM2 health states

Health utility values for the DM1 and DM2 health states were taken from external sources. The utility value for the DM1 state was based on a previous mapping exercise applied in NICE TA654 (osimertinib for untreated EGFRm NSCLC).[21] Within this appraisal, EORTC QLQ-C30 data collected in the FLAURA trial[39] were mapped to the EQ-5D-3L using a function reported by Young *et al*.[76] The model used to inform TA654 applied a utility value of 0.794 to the progression-free (PF) health state; this same value is applied in the DM1 state in the adjuvant osimertinib model.

The utility value for the DM2 health state was taken from a longitudinal cohort study undertaken at the Princess Margaret Cancer Centre in Toronto, Canada (Labbé *et al.*[69]). This study included 1,571 EQ-5D-3L estimates from 475 outpatients with metastatic lung cancer across various disease states. The company's model applies a utility value of 0.64; this relates to the estimated EQ-5D-3L utility for the "progressing" state valued using the UK tariff.

Summary of health state utility values applied in the company's economic model

The utility values applied in the model are summarised Table 38. All health state utility values were adjusted for age using Ara and Brazier.[73]

Table 38: Utility values applied in the company's model

Health state	Mean utility	SE	Source
DF	0.825	0.018	ADAURA[36] (SF-36 mapped to EQ-5D-3L). The same utility value is assumed for both DF and LRR states
LRR	0.825	0.018	
DM1	0.794	0.0069	FLAURA[39] (EORTC QLQ-C30 mapped to EQ-5D-3L).
DM2	0.640	0.03	Labbé *et al.*[69] (reported UK EQ-5D estimate)

SE - standard error; DF - disease-free; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; SF-36 - Short Form 36; EQ-5D-3L - Euroqol 5-Dimensions 3-Level; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

Disutilities associated with AEs

Whilst the company's RMME models include a covariate for AEs, the company's economic model instead uses estimates of disutilities associated with AEs obtained from external sources: Nafees *et al.*[77] and NICE TA653.[78] Nafees *et al.* is a standard gamble study of various NSCLC states, valued by 100 members of the general public. The disutilities derived from NICE TA653 (osimertinib for treating EGFR T790M mutation-positive advanced NSCLC) appear to be based on an analysis of data collected

within the AURA3 trial.[62] The model assumes that the events of prolonged QT and ejection fraction decreased are not associated with a loss in HRQoL. Estimates of the frequency of Grade ≥3 AEs were taken from ADAURA.[36] Based on the AE frequencies and their estimated disutilities, the model applies QALY losses of -0.0023 and -0.0001 in the adjuvant osimertinib and active monitoring groups, respectively. These QALY losses are assumed to apply for one month and are applied in the first model cycle only.

Table 39: Disutilities associated with AEs applied in the company's model

AE	Disutility			AE frequency		
	Mean disutility	SE	Source	Adjuvant osimertinib	Active monitoring	Source
Paronychia*	-0.0325	-0.0016	Nafees *et al.*[77]	[redacted]	[redacted]	ADAURA[36] (DCO April 2022)
Decreased appetite	-0.05	-0.0025	TA653[78] (AURA3[62])	[redacted]	[redacted]	
Diarrhoea	-0.0468	-0.0023	Nafees *et al.*[77]	[redacted]	[redacted]	
Stomatitis†	-0.05	-0.0025	TA653[78] (AURA3[62])	[redacted]	[redacted]	
ECG QT prolonged	0	0	Assumption	[redacted]	[redacted]	
Ejection fraction decreased	0	0	Assumption	[redacted]	[redacted]	

AE - adverse event; SE - standard error; TA - Technology Appraisal
**Assumed to be the same as rash*
†*Assumed to be the same as decreased appetite*

5.2.4.4 Resource use and costs

The model includes costs associated with: (i) drug administration (first cycle and subsequent cycles) and monitoring; (ii) drug acquisition; (iii) disease management; (iv) management of AEs and (v) end-of-life care. The costs applied in the company's model are summarised in Table 40; these are described in further detail in the subsequent text. It should be noted that the original version of the company's executable model includes several errors relating to costs; the text below relates to the cost assumptions as detailed in the CS.[2] Model errors are discussed in more detail in Section 5.3.6. Model results including the correction of these errors are provided in Section 5.4.

Table 40: Summary of costs applied in the company's model

Cost component (per month, unless otherwise stated)	Adjuvant osimertinib	Active monitoring
Acquisition costs (adjuvant)*	Osimertinib: [redacted]	N/a
Administration and monitoring costs (adjuvant)*	Osimertinib: £200.86	N/a
LRR drug acquisition costs	PDC plus radiotherapy: £2,333.36 Radiotherapy only: £5,444.13 (monitoring costs inclusive)	PDC plus radiotherapy: £2,333.36 Radiotherapy only: £5,444.13 (monitoring costs inclusive)
LRR drug administration costs	PDC: Initial cycle £584.64; subsequent cycles £463.78	PDC: Initial cycle £584.64; subsequent cycles £463.78
DM1 drug acquisition costs	PDC (100% relapsed patients before 48 months, 50% relapsed patients after 48 months): £372.52 Osimertinib (50% relapsed patients after 48 months): [redacted]	Osimertinib (83% patients with relapse): [redacted] Early TKI (17% patients with relapse): £1220.29†
DM1 drug administration and monitoring costs	Osimertinib: £396.82 (all cycles) PDC: Initial cycle £712.98; Subsequent cycles £565.58	Osimertinib: £396.82 (all cycles) Early TKI: Initial cycle £396.82; Subsequent cycles £411.82†
DM2 drug acquisition costs	Docetaxel (patients treated with PDC in DM1): £18.54 PDC (80% of patients retreated with osimertinib in DM1): £372.52 ABCP (20% of patients retreated with osimertinib in DM1): £5518.88 (atezolizumab), £2,773.62 (bevacizumab), £36.00 (carboplatin), £28.08 (paclitaxel)	PDC (80% of patients treated with either osimertinib or TKI in DM1): £372.52 ABCP (20% of patients treated with either osimertinib or TKI in DM1): £5,518.88 (atezolizumab), £2,773.62 (bevacizumab), £36.00 (carboplatin), £28.08 (paclitaxel)
DM2 drug administration and monitoring costs	Docetaxel: Initial cycle £713.89; subsequent cycles £566.49 PDC or ABCP: Initial cycle £712.98; subsequent cycles £565.58	PDC or ABCP: Initial cycle £712.98; subsequent cycles £565.58
Disease management costs	DF: £280.20; LRR: £552.51; DM1: £718.58; DM2: £718.58	
CNS metastases costs (once-only cost on progression to DM1) ‡	£18,616 (weighted cost of stereotactic radiotherapy and whole-brain radiotherapy)	
CNS metastases management costs	£477.21	
AE costs (once-only)	£120.63‡	£12.74
End-of-life care (once-only)	£2,801.99	

LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; CNS - central nervous system; PDC - pemetrexed plus cisplatin; N/a - not applicable; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel

** Maximum treatment duration = 3 years*

†Includes weighted erlotinib, gefitinib and afatinib costs amongst TKI-treated patients

‡Subject to an error whereby cost calculations in the model exclude the cost of decreased ejection fract

Drug acquisition costs and radiotherapy fraction costs

The costs of drug treatments given in the adjuvant setting and for loco-regional and distant recurrence are summarised in Table 41. All drugs were costed according to a monthly cycle duration. The model includes the PAS discount for osimertinib in the adjuvant indication.

Table 41: Costs of drug acquisition and radiotherapy included in the company's model, includes PAS discount for osimertinib

Drug	Admin. Route	Dose per admin.	RDI	Criteria for discontinuation	Cost per model cycle	Source
Adjuvant treatment						
Osimertinib	Oral	80mg (daily)	[redacted]	Maximum 3 years, progression, or death	[redacted]	BNF[38]
Chemoradiotherapy in LRR						
Pemetrexed	IV	500mg/m^2	100%	2.8 model cycles,* progression, or death	£2,333.36	BNF[38]
Cisplatin	IV	75mg/m^2	100%			eMIT[79]
Radiotherapy§	-	55 Gray (20 fractions in total)	-			NHS Reference Costs 2021/22[80]
Radiotherapy in LRR						
Radiotherapy§	-	55 Gray (20 fractions in total)	-	1 model cycle (one-off cost)	£5,411.43	NHS Reference Costs 2021/22[80]
Drug treatments for distant metastases						
Osimertinib	Oral	80mg (daily)	[redacted]	Progression or death	[redacted]	BNF[38]
Erlotinib	Oral	150mg	[redacted]	Progression or death	£98.53	eMIT[79]
Gefitinib	Oral	250mg	[redacted]	Progression or death	£283.75	eMIT[79]
Afatinib	Oral	40mg	[redacted]	Progression or death	£2,157.62	BNF[38]
Pemetrexed	IV	500mg/m^2	100%	3.4 model cycles,† progression, or death	£352.26	eMIT[79]
Cisplatin	IV	75mg/m^2	100%	3.4 model cycles,† progression, or death	£20.27	eMIT[79]
Docetaxel	IV	75mg/m^2	100%	2.8 model cycles* or death	£18.54	eMIT[79]
Atezolizumab	IV	1,200mg	100%	Death	£5,518.88	BNF[38]
Bevacizumab	IV	15mg/kg	100%	Death	£2,773.62	BNF[38]
Carboplatin	Oral	692mg	100%	2.8 model cycles‡ or death	£36.00	eMIT[79]
Paclitaxel	Oral	200mg/m^2	100%	2.8 model cycles‡ or death	£28.08	eMIT[79]

RDI - relative dose intensity; IV - intravenous; LRR - loco-regional recurrence; BNF - British National Formulary; eMIT - electronic Market Information Tool; Admin. - administration; PAS - Patient Access Scheme

** Corresponds to four 21-day treatment cycles*

† Corresponds to five 21-day treatment cycles

‡ Corresponds to three 21-day treatment cycles, although this aspect of the model is subject to a minor error (see Section 5.3.6, critical appraisal point [i])

§Including the costs of planning meeting for radiotherapy

Drug acquisition costs - adjuvant osimertinib

The list price per pack of 30 x 80mg osimertinib tablets (30 days' supply) is £5,770. The company has agreed a PAS for adjuvant osimertinib of [redacted]; the cost per pack including this discount is [redacted]. Within the economic model, total acquisition costs for adjuvant osimertinib are calculated using the empirical Kaplan-Meier function for TTD from the intervention arm of ADAURA[36] (see Figure 34), the RDI for osimertinib and the acquisition cost of adjuvant osimertinib (including the PAS). The model assumes a maximum treatment duration of 3-years for osimertinib in the adjuvant setting; all patients are assumed to discontinue treatment at this timepoint. An RDI of [redacted] is applied for osimertinib in both the adjuvant and metastatic settings, based on FLAURA.[39] The active monitoring comparator group does not include any drug treatment costs unless the patient experiences subsequent relapse. The EAG notes that TTD is not structurally linked to any clinical outcomes in the model (i.e., if all patients die in the first monthly cycle, the net acquisition cost of osimertinib remains unchanged).

Figure 34: Time to treatment discontinuation from ADAURA (reproduced from CS, Figure 47)

[redacted]

DCO April 2022

Costs of drug acquisition and radiotherapy - treatments for loco-regional recurrence

Amongst patients with loco-regional recurrence, 82% are assumed to receive chemoradiotherapy which is assumed to comprise 2.8 model cycles of PDC plus 20 fractions of radiotherapy. The remaining 18% of patients are treated with 20 fractions of single-modality radiotherapy. The list prices for 500mg IV pemetrexed and 75mg IV cisplatin are £352.16 and £20.27 per cycle, respectively.[38, 79] The model assumes that vial sharing is permitted for both pemetrexed and cisplatin. The cost per radiotherapy fraction (assumed to be intraluminal brachytherapy) is £211.85, and each patient is assumed to require one planning meeting for radiotherapy which is associated with a unit cost of £1,176.46. Radiotherapy costs were taken from NHS Reference Costs 2021/22.[80] The total cost of chemoradiotherapy is £2,333.36 per monthly cycle, and the total one-off cost of single-modality radiotherapy is £5,411.43.

Drug acquisition costs - treatments for distant metastases

In the active monitoring group, the model assumes that 83% of patients with distant metastases receive osimertinib and 17% receive early TKIs (5% erlotinib, 3% gefitinib and 9% afatinib) as first-line treatment, based on 2023 Ipsos market share data. Subsequently, 80% of these patients undergo PDC (3.4 model cycles) and 20% receive ABCP as second-line therapy. Within the adjuvant osimertinib group, the model assumes that all patients who experience distant relapse within 48 months and 50% of those who relapse after 48 months receive first-line PDC (3.4 model cycles) followed by second-line docetaxel (2.8 model cycles), whilst the remaining 50% of patients who relapse after 48 months receive re-treatment with osimertinib at first-line, followed by either PDC (in 80% of cases for 3.4 model cycles) or ABCP (in 20% of cases) at second-line. The assumed proportion of patients who are re-treated with osimertinib in DM1 is based on the company's previous assumption made during TA761.[20] The model includes the same PAS discount for osimertinib in the adjuvant and metastatic settings, as described above. The per-cycle costs of 150mg oral erlotinib, 250mg oral gefitinib, and 40mg oral afatinib are £98.53, £283.75, and £2,157.62, respectively.[38, 79] The per-cycle costs of PDC are the same as those applied in the LRR state. The cost of 75mg IV docetaxel is based on the list price of £18.54 per model cycle.[79] For the ABCP regimen, the list prices for 1,200mg IV atezolizumab, 15mg IV bevacizumab, 692mg oral carboplatin and 200mg oral paclitaxel are £5,518.88, £2,773.62, £36.00 and £28.08 per cycle, respectively.[38, 79] The company's base case model assumes that vial sharing is permitted for IV drugs. Drug wastage costs are not included for any therapy.

Drug administration and monitoring costs

Table 42 summarises the drug administration and monitoring costs applied in the company's model. The model assumes an administration cost of osimertinib and early TKIs of £10.60 per cycle, based on the costs of pharmacy dispensing from the Personal Social Services Research Unit (PSSRU).[81] Drug administration costs for chemotherapy-including regimens (PDC, docetaxel and ABCP) include an outpatient attendance for the delivery of chemotherapy, with separate costs applied for initial and subsequent attendances, and premedication with dexamethasone for 3 days (PDC and ABCP - 8mg per day; docetaxel - 16mg per day). The unit costs for outpatient attendances were taken from NHS Reference Costs 2021/22.[80] Dexamethasone premedication costs were based on prices listed in the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT).[79]

Drug monitoring costs are applied in each model cycle. The model assumes that all patients undergo liver function, renal function, and complete blood count tests, whilst patients receiving osimertinib or early TKIs require additional ECGs and echocardiograms. The model assumes that the monitoring costs for osimertinib-treated patients in the metastatic setting are twice as high as those in the adjuvant setting. Unit costs were taken from NHS Reference Costs 2021/22.[80]

Table 42: Drug administration, monitoring and premedication costs

Cost type	Component	Unit cost			Source
		Osimertinib/ erlotinib/ gefitinib/ afatinib	PDC/ ABCP	Docetaxel	
Administration costs	Pharmacist dispensing	£53.00 per hour (£10.60 per model cycle)	-	-	PSSRU[81]
	Initial outpatient attendance for chemotherapy	-	£485.23	£485.23	NHS Reference Costs 2021/22[80]
	Subsequent outpatient attendance for chemotherapy	-	£383.54	£383.54	
	8mg dexamethasone	-	£0.63	-	eMIT[79]
	16mg dexamethasone	-	-	£1.26	eMIT[79]
Monitoring costs	Liver function test	£1.55	£1.55	£1.55	NHS Reference Costs 2021/22[80]
	Renal function test	£1.55	£1.55	£1.55	
	Complete blood count	£2.96	£2.96	£2.96	
	ECG	£159.36	-	-	
	Echocardiogram	£363.09	-	-	
Total cycle cost per monthly cycle (initial cycle)		£396.82 £425.17 (for afatinib)	£712.98	£713.89	-
Total cycle cost per monthly cycle (subsequent cycles)		£396.82 £425.17 (for afatinib)	£565.58	£566.49	-

PDC - pemetrexed plus cisplatin; ABCP- atezolizumab plus bevacizumab, carboplatin and paclitaxel; PSSRU - Personal Social Services Research Unit; eMIT - electronic Market Information Tool; ECG - electrocardiogram

Disease management costs

Table 43 summarises the per-cycle disease management costs assumed for each of the four alive health states in the company's model. Resource use estimates for each state were taken from the LuCaBIS study of patients with resected IB-IIIA NSCLC during adjuvant chemotherapy and following loco-regional recurrence or distant metastases (Andreas *et al*.[19]). In the DF health state, the mean resource use for patients on and off adjuvant chemotherapy in Andreas *et al.* was used. Based on clinical expert opinion, oncology visits for patients not on adjuvant chemotherapy in the DF health state were excluded, as was radiotherapy for disease management in all health states. As Andreas *et al*. did not differentiate between first- and second-line treatments for metastases, the company's model assumes the same level of resource use for both the DM1 and DM2 health states. Unit costs for each resource use item were based on NHS Reference Costs 2021/22.[80] The company's model applies the same costs to the health states for both the intervention and comparator groups.

Table 43: Disease management resource use and costs applied in the economic model

Resource Type	Frequency per model cycle			Unit cost	Total cost per model cycle		
	DF	LRR	DM1/DM2		DF	LRR	DM1/DM2
Hospitalisation	0.069	0.120	0.207	£827.06	£57.06	£98.91	£171.19
Oncologist visits (subsequent)	0.086	0.635	0.609	£163.79	£14.04	£103.97	£99.82
Surgeon visits	0.151	0.184	0.149	£242.72	£36.54	£44.66	£36.28
Pulmonologist/ respiratory physician (subsequent)	0.153	0.239	0.115	£194.75	£29.72	£46.58	£22.39
Other specialist visit	0.146	0.230	0.149	£163.79	£23.90	£37.67	£24.48
A&E	0.065	0.120	0.161	£157.62	£10.22	£18.85	£25.38
CT scans	0.079	0.202	0.264	£142.47	£11.32	£28.83	£37.68
MRI	0.044	0.092	0.138	£243.18	£10.68	£22.37	£33.56
PET scans	0.046	0.092	0.230	£665.48	£30.61	£61.22	£153.05
PET-CT scans	0.065	0.092	0.115	£722.11	£46.80	£66.43	£83.04
Ultrasound	0.069	0.092	0.149	£84.95	£5.86	£7.81	£12.70
Nuclear medicine studies	0.021	0.092	0.115	£165.38	£3.46	£15.21	£19.02
Total cost	-	-	-	-	**£280.20**	**£552.51**	**£718.58**

DF - disease-free; LRR - loco-regional recurrence: DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; A&E - Accident and Emergency; CT - computerised tomography; MRI - magnetic resonance imaging; PET - positron emission tomography

Additional disease management costs were included for a proportion of patients who develop CNS metastases (see Table 44). Estimates of the proportion of patients who experience CNS metastases were taken from the intervention and comparator arms of ADAURA.[36] Estimates of the additional resources required to manage CNS metastases were taken from TA536 (alectinib for untreated anaplastic lymphoma kinase [ALK]-positive advanced non-small-cell lung cancer).[82] Unit costs were taken from NHS Reference Costs 2021/22[80] and the PSSRU.[81] These costs are applied to patients whilst in the DM1 and DM2 states. The company's model also assumes that patients who develop CNS metastases will incur a once-only cost of radiotherapy upon progression to DM1. The model assumes that 50% of patients with CNS metastases will receive six doses of stereotactic radiotherapy, with the remaining 50% receiving whole-brain radiotherapy. This assumption was based clinical expert opinion received by the company and a publication by the Royal College of Radiologists.[89] Unit costs for stereotactic radiotherapy were taken from NHS Reference Costs 2021/22, whilst the unit cost for whole-brain radiotherapy was based on TA536 and was inflated to 2023 prices using the NHS Cost Inflation Index (NHSCII).

Table 44: CNS metastases disease management costs applied in the company's model

CNS metastasis cycle costs					
Resource type	**Frequency per model cycle**	**Unit cost**	**Total costs**	**Frequency source**	**Unit cost source**
GP visit	0.92	£41.00	£37.72	TA536[82]	PSSRU[81]
Consultant/ oncologist outpatient visit	0.64	£163.79	£104.92		NHS Reference Costs 2021/22[80]
Cancer nurse visit	1.38	£119.00	£164.21		
Full blood test	1.38	£2.96	£4.08		
Biochemistry	1.38	£1.55	£2.14		
CT scan	0.43	£160.38	£68.23		
MRI scan	0.32	£243.18	£78.30		
X-ray	0.46	£38.28	£17.61		
Total cost	**-**		**£477.21**		
CNS metastases once-only costs (applied on progression to DM1)					
Resource Type	**Frequency**	**Unit cost**	**Total costs**	**Frequency source**	**Unit cost source**
Stereotactic radiotherapy*	6.00	£5,456.83	£16,370.49	RCR report[89] and clinical opinion[85]	NHS Reference Costs 2021/22[80]
Whole brain radiotherapy*	1.00	£4,491.28	£2,245.64		TA536 ERG report[82]
Total cost	-	-	**£18,616.13**	-	-

CNS - central nervous system; GP - general practitioner; CT - computerised tomography; MRI - magnetic resonance imaging; PSSRU - Personal Social Services Research Unit; ERG - Evidence Review Group
**Each resource type is applied to 50% of patients with CNS metastases*

AE management costs

Table 45 summarises the frequency of AEs and the assumed cost of managing each event, as applied in the company's model. AE frequencies were taken from ADAURA;[36] only Grade 3/4 events that occurred in two or more patients in either treatment arm in the trial were included. Unit costs were taken from NHS Reference Costs 2021/22.[80] All AE management costs are applied once-only during the first model cycle. AEs associated with downstream treatments for loco-regional and distant recurrence are not explicitly included in the model. The EAG notes that the cost of decreased ejection fraction is erroneously excluded from the company's cost calculations in the model.

Table 45: AE frequencies and costs

AE	Frequency - adjuvant osimertinib	Frequency - active monitoring	Unit cost	Total costs - adjuvant osimertinib	Total costs - active monitoring
Paronychia	[redacted]	[redacted]	£2,011.95	£18.11	£0.00
Decreased appetite	[redacted]	[redacted]	£2,639.41	£15.84	£0.00
Diarrhoea	[redacted]	[redacted]	£1,847.25	£38.79	£5.54
Stomatitis	[redacted]	[redacted]	£1,273.81	£19.11	£0.00
ECG QT prolonged	[redacted]	[redacted]	£2,399.26	£28.79	£7.20
Ejection fraction decreased	[redacted]	[redacted]	£3,201.01	£19.21	£9.60
Total costs*	-	-	-	**£139.84**	**£22.34**

AE - adverse event; ECG - electrocardiogram
** Total costs reported in this table include a correction made by the company*

End-of-life care costs

The cost of end-of-life care was applied as a once-only cost of £2,801.99 to patients at the point of death. This estimate was based on the proportion of patients who require end-of-life care in either hospital, in a hospice or at home, based on a published study by Brown *et al.*[90] Costs were based on NHS Reference Costs 2021/22, the PSSRU[81] and a report by Marie Curie Cancer Care.[83]

EGFR mutation testing costs

The company's executable model does not include the costs of EGFR mutation testing. The CS[2] states that EGFR mutation testing is done routinely in the UK for patients with NSCLC.

5.2.5 Model evaluation methods

The CS[2] presents a base case incremental cost-effectiveness ratio (ICER) for adjuvant osimertinib versus active monitoring based on the point estimates of parameters. Results are also presented using the probabilistic version of the model, based on 1,000 Monte Carlo simulations. The results of the company's probabilistic sensitivity analysis (PSA) are presented using a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs). The results of the company's deterministic sensitivity analyses (DSAs) are presented using a tornado plot and a summary table. The CS also reports the results of scenario analyses which explore the impact of alternative assumptions regarding: radiotherapy costs; re-treatment timepoints; alternative parametric survival distributions for TP1 and/or TP2; the cure warm-up period; discount rates for cured patients and health state utility values.

5.2.6 Severity weighting

The CS[2] does not include any discussion of severity weighting. Based on the York Shortfall calculator,[91] the active monitoring group of the company's model suggests an absolute shortfall of 4.62 QALYs and a proportional QALY shortfall of 39.45%. This suggests a severity modifier of 1.0.

5.2.7 Company's model results

Central estimates of cost-effectiveness

This section presents the results of the company's original model, as reported in the CS.[2] Table 46 presents the central estimates of cost-effectiveness for adjuvant osimertinib versus active monitoring based on the company's original model. The probabilistic version of the company's model suggests that adjuvant osimertinib is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] compared with active monitoring; this corresponds to an ICER of £18,378 per QALY gained. The deterministic version of the model suggests a slightly higher ICER of £18,967 per QALY gained.

Table 46: Company's cost-effectiveness results, adjuvant osimertinib versus active monitoring

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Probabilistic model							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£18,378**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£18,967**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental
** Undiscounted*
†Generated by the EAG by modifying the company's PSA sub-routine

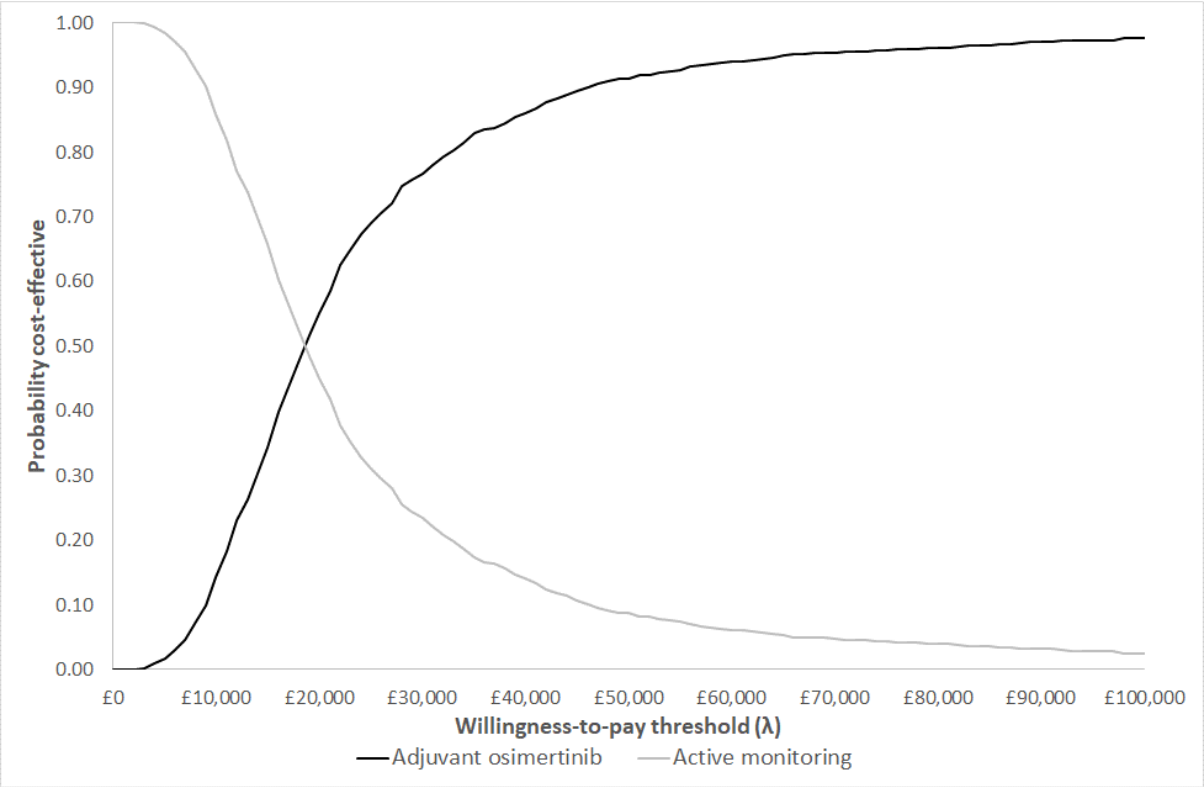
Company's PSA results

The results of the company's PSA are presented in the form of a cost-effectiveness plane in Figure 35; the CEACs are shown in Figure 36. Assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the company's model suggests that the probability that adjuvant osimertinib generates more net benefit than active monitoring is approximately 0.55 and 0.77, respectively.

Figure 35: Cost-effectiveness plane, adjuvant osimertinib versus active monitoring (generated by the EAG using the company's model)

QALY - quality-adjusted life year

Figure 36: CEACs, adjuvant osimertinib versus active monitoring (generated by the EAG using the company's model)

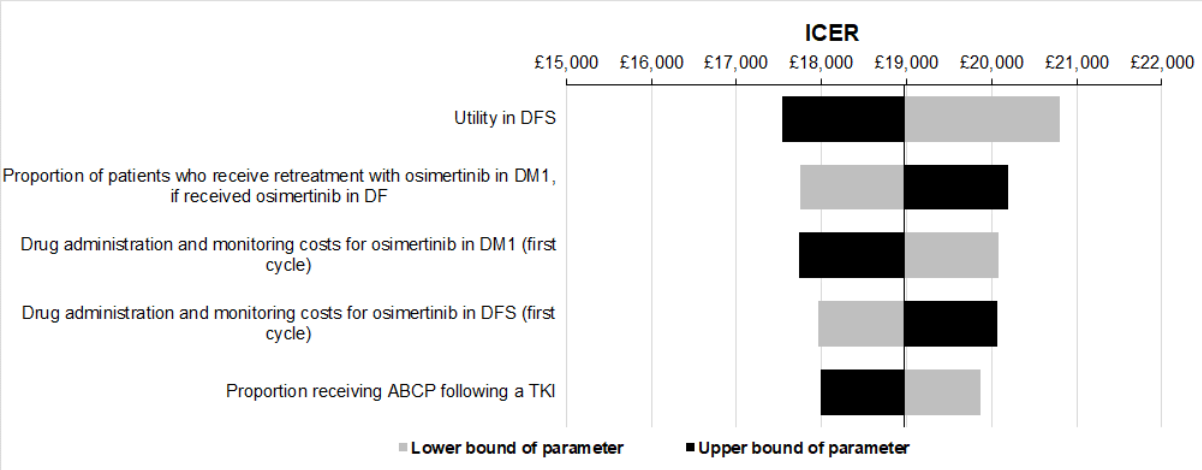


Company's DSA results

Figure 37 presents the results of the company's DSAs in the form of a tornado plot. These analyses indicate that the ICER for adjuvant osimertinib is not particularly sensitive to any of the parameter

values tested. Across all of the DSAs conducted, the highest ICER reported for adjuvant osimertinib versus active monitoring is £20,805 per QALY gained.

Figure 37: Tornado diagram, adjuvant osimertinib versus active monitoring (generated by the EAG using the company's model)



ICER - incremental cost-effectiveness ratio; DFS - disease-free survival; DM - distant metastases; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel; TKI - tyrosine kinase inhibitor

Company's scenario analysis results

Table 47 presents the results of the company's scenario analyses. As shown in the table, the ICER is estimated to range from £11,405 per QALY gained (SA7: osimertinib cure warm-up period from 36 to 96 months) to £24,710 per QALY gained (SA4: alternative survival models used in TP1). The EAG notes that all of the scenarios tested include a warm-up period which assumes that a proportion of patients of osimertinib-treated patients are cured from 48 months or earlier.

Table 47: Company's scenario analysis results, adjuvant osimertinib versus active monitoring

Scenario	Adjuvant osimertinib versus active monitoring			
	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case (deterministic)	[redacted]	[redacted]	[redacted]	£18,967
SA1: Stereotactic radiotherapy 66%, 1 dose & Whole brain radiotherapy 34%, 2 doses	[redacted]	[redacted]	[redacted]	£18,499
SA2: Osimertinib retreatment after 42 months	[redacted]	[redacted]	[redacted]	£20,199
SA3: Osimertinib retreatment after 60 months	[redacted]	[redacted]	[redacted]	£16,506
SA4: TP1 (DF to LRR) distributions: Osimertinib - Weibull; Active monitoring - generalised gamma	[redacted]	[redacted]	[redacted]	£24,710
SA5: TP2 (DF to DM1) distributions: Osimertinib - log-normal; Active monitoring - generalised gamma	[redacted]	[redacted]	[redacted]	£15,841
SA6: TP1: Osimertinib - Weibull; Active monitoring - generalised gamma and TP2: Osimertinib - log-normal; Active monitoring - generalised gamma	[redacted]	[redacted]	[redacted]	£21,010
SA7: Osimertinib cure warm-up period applied from 36 months to 96 months	[redacted]	[redacted]	[redacted]	£11,405
SA8: QALY discount of 1.5% to cured patients	[redacted]	[redacted]	[redacted]	£15,526
SA9: Health state utilities from Andreas *et al.*,[19] (DF=0.72; LRR=0.62; DM1 & DM2=0.67)	[redacted]	[redacted]	[redacted]	£20,926

Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; TP - transition probability; DF - disease-free; LRR - loco-regional recurrence; DM - distant metastases

5.3 Critical appraisal of the company's economic analyses

This section presents the EAG's critical appraisal of the company's original economic model, as described in the CS.[2] Section 5.3.1 summarises the EAG's methods for the critical appraisal of the company's model. Section 5.3.2 provides a summary of the key issues and the Appraisal Committee's conclusions from TA761.[20] Sections 5.3.3 and 5.3.4 describe the EAG's verification of the company's current model and the correspondence between the CS, the model inputs and the original sources of those inputs. Section 5.3.5 describes the extent to which the company's current economic analysis adheres to the NICE Reference Case.[92] Section 5.3.6 presents the EAG's critical appraisal of the current model.

As part of their response to clarification questions from the EAG,[42] the company submitted two revised versions of the model which include the correction of several programming errors. The second revised model and its results are summarised separately in Section 5.4.

5.3.1 Critical appraisal methods

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[93, 94]
- Scrutiny and discussion of the company's model by the EAG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation. The EAG also checked that errors present in the original version of the company's model used in TA761 were not present in the model for the current appraisal.
- Examination of the correspondence between the description of the model reported in the CS^2 and the company's executable model.
- Where possible, checking of parameter values used in the company's model against their original data sources.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's executable model.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.2 Summary of key issues discussed in TA761, including the Appraisal Committee's conclusions

Box 1 summarises the key issues relating to the company's earlier model, as discussed in the TA761 guidance document,[20] including the Appraisal Committee's conclusions.

Box 1: Key issues and Appraisal Committee's conclusions in TA761

Use of osimertinib as first-line treatment for distant metastases (with active monitoring, and in the re-treatment setting)

- NHS England (NHSE) stated that re-treatment with osimertinib would be permitted, but that the proportion of patients who would be re-treated was uncertain.
- The company acknowledged uncertainty around the proportion of patients receiving osimertinib as first-line therapy for distant metastases in the active monitoring group, and as re-treatment in the adjuvant osimertinib group.
- The Appraisal Committee preferred to assume that 80% of patients under active monitoring would receive osimertinib as first-line therapy for distant metastases, based on the latest prescribing data.

Long-term benefits of treatment on OS

- Owing to data immaturity, the Appraisal Committee stated that the size of any potential benefit on OS was uncertain. It was also uncertain to what extent a benefit in DFS would translate into a benefit in OS.
- The choice of parametric survival model, particularly for TP2 (DF to DM1), had a significant effect on the model results.

Modelling cure

- The company's base case model included a single cure timepoint of 5 years in both treatment groups. This was included as part of the EAG's preferred optimistic scenario.
- Based on clinical advice, the EAG also presented a preferred pessimistic scenario which applied cure timepoint of 5 years for the active monitoring group and 8 years for the adjuvant osimertinib group.
- The Appraisal Committee concluded that the company's model structure was acceptable, but commented that more formal modelling of cure (e.g., using MCMs) may address uncertainty.

3-year stopping rule for adjuvant osimertinib

- The Appraisal Committee concluded that the 3-year stopping rule is acceptable. Patient experts stated some may wish to continue treatment with adjuvant osimertinib for longer if their disease had not progressed.

Use of external evidence from FLAURA

- The Appraisal Committee acknowledged people who relapse under active monitoring may have better outcomes compared with newly diagnosed patients enrolled in FLAURA.

Utility values

- The Appraisal Committee considered the utility values applied in the company's model to be acceptable for decision-making.

Decision modifiers

- The Appraisal Committee concluded that NICE's End of Life criteria did not apply.

ICERs considered in decision-making

- The company's and the ERG's analyses included varying: (i) the cure timepoint, (ii) the proportion of patients receiving osimertinib in DM1, (iii) the parametric model for DF to DM1, and (iv) the osimertinib re-treatment proportion.

5.3.3 Model verification by the EAG

Table 48 presents a comparison of the results of the deterministic version of the company's original model and the EAG's double-programmed model. As shown in the table, the results obtained from the EAG's rebuilt model are very similar to those generated using the company's model. However, the EAG's double-programming exercise revealed a number of programming errors; these are discussed in detail in Section 5.3.6.

Table 48: Comparison of results generated using the company's original model and the EAG's double-programmed model, excludes correction of errors

Outcome	Company's model		EAG's double-programmed model	
	Adjuvant osimertinib	Active monitoring	Adjuvant osimertinib	Active monitoring
LYGs*	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]
ICER	**£18,967**		**£18,953**	

EAG - External Assessment Group; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

5.3.4 Correspondence between model inputs and original source data

Where possible, the EAG checked the company's model input values against their original sources. The parameters of the parametric survival models used to estimate transition probabilities were generated from analyses of IPD or pseudo-IPD from the ADAURA, FLAURA and IMPower150 trials;[36, 39, 40] these data were not made available to the EAG, and as such, the EAG cannot verify that these analyses have been undertaken appropriately. The EAG was able to identify most of the other model parameter values including the utility and disutility values, AE rates and most of the unit costs. The EAG was unable to identify the costs of whole brain radiotherapy or PET-CT scans. This is likely to be a minor issue. In addition, the EAG notes that the AIC and BIC statistics in the company's economic model for TP1 and TP2 for the osimertinib arm and TP8 for the erlotinib/gefitinib arm are different from the values presented in the CS. The company's response to additional follow-on questions from the EAG stated that the values of TP1 and TP8 presented in the CS are correct and these were used to inform the selection of parametric survival models. For TP2, the company provided a corrected table and clarified that the final model selection was not affected by these errors.

5.3.5 Adherence of the company's model to the NICE Reference Case

Table 49 summarises the extent to which the company's economic analysis adheres to the NICE Reference Case.[92] Overall, the EAG believes that the company's model is partly in line with the Reference Case. The most pertinent deviations are: (i) subgroup analyses by disease stage have not been conducted, and (ii) adjuvant chemotherapy is listed as a comparator in the NICE scope, but this option has not been included as a comparator in the company's model.

Table 49: Adherence of the company's economic model to the NICE Reference Case

Element	Reference case	EAG comments
Defining the decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is generally in line with the final NICE scope.[33] Economic subgroup analyses by stage are not presented.
Comparator(s)	As listed in the scope developed by NICE	The company's model includes active monitoring as the sole comparator: this is not consistent with the final NICE scope[33] which also lists adjuvant platinum-based chemotherapy as a comparator. However, the EAG's clinical advisors did not consider chemotherapy to be a relevant comparator for osimertinib.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The economic analysis adopts an NHS and PSS perspective, including health effects on patients. Impacts on caregivers are not included.
Perspective on costs	NHS and PSS	Costs include those borne by the NHS and PSS.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained for adjuvant osimertinib versus active monitoring.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 37-year (lifetime) time horizon.
Synthesis of evidence on health effects	Based on systematic review	DFS outcomes for adjuvant osimertinib and active monitoring are informed by the ADAURA trial:[36] this is the pivotal trial of osimertinib identified from the company's SLR. Outcomes for treatments for LRR and DM are based on data from CancerLinQ,[71] FLAURA[39] and IMPower150.[40] The EAG considers these data sources to be relevant to the decision problem.
Measuring and valuing health	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health state utility values are based on EQ-5D-3L estimates from ADAURA[36] (mapped from the SF-36), EQ-5D-3L estimates from FLAURA[39] (mapped from the EORTC QLQ-C30) and published EQ-5D-3L estimates from the literature (Labbé *et al*.[69]). Disutilities associated with AEs are based published literature (Nafees *et al.*[77], valued using the standard gamble technique) and NICE TA653[78] (elicitation/ valuation method unclear).
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied.

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	Drug costs are valued at current prices. Other resource costs are valued using estimates from NHS Reference Costs 2021/22[80] and the PSSRU.[81]
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

EAG - External Assessment Group; NHS - National Health Service; PSS - Personal Social Services; PSSRU - Personal Social Services Research Unit; QALY - quality-adjusted life year; EQ-5D-3L - Euroqol 5 Dimensions (3-level); EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer quality of life questionnaire; NICE - National Institute for Health and Care Excellence; TA - Technology Appraisal; HRQoL - health-related quality of life; LRR - loco-regional recurrence; DM - distant metastasis

5.3.6 Key issues identified from the EAG's critical appraisal

Box 2 summarises the main issues identified within the EAG's critical appraisal of the company's original economic model for the current appraisal. These issues are discussed in further detail in the subsequent sections. Where relevant, the EAG draws reference to key issues raised by the ERG in TA761, as well as the Appraisal Committee's preferred conclusions as described in the final guidance document for the previous appraisal (see Box 1).[20]

Box 2: Main issues identified from the EAG's critical appraisal

(1) Model errors
(2) Exclusion of adjuvant chemotherapy as a comparator for adjuvant osimertinib
(3) Uncertainty around long-term DFS and OS outcomes for adjuvant osimertinib, including potential curative effects
(4) Issues relating to the company's survival analysis
(5) Unconventional approach to modelling cure
(6) Uncertainty surrounding the use of osimertinib in the first-line metastatic setting (as re-treatment and as treatment for relapsed active monitoring patients)
(7) Use of external data from FLAURA and the need for calibration
(8) Uncertainty relating to utility values
(9) Exclusion of EGFR testing costs from the company's model
(10) Inclusion of non-reference case discount rates in company's scenario analysis
(11) Absence of an economic subgroup analysis by disease stage

(1) Model errors

The EAG's double-programming exercise and additional cell-checking undertaken by the EAG revealed several errors in the company's original executable model. Some of these issues were identified and corrected by the EAG during TA761[20] and reintroduced in the current model, whilst others appear to have been introduced through further model adaptations made by the company since the previous

appraisal. These errors are described below. With the exception of error (b-iii) and (c), these errors were identified before the EAG submitted the clarification letter.

As part of their clarification response,[42] the company provided an updated version of the model which addresses the majority of these errors (see Section 5.4).

(a) Estimation of general population mortality risks

The company's model uses general population life tables[41] in three ways: (a) to determine per-cycle mortality risks in patients who are considered cured, (b) to inform the transition probabilities of DF to dead (TP3) and LRR to dead (TP5), and (c) to constrain the per-cycle mortality risk for all patients in the DM1 and DM2 health states. Within the calculations used to derive these general population mortality constraints, the model assumes that the proportionate split of men and women remains constant at every age. However, the general population life tables indicate that men and women have different age-specific risks of death. The EAG believes that it would be more appropriate to estimate general population mortality risks using a weighted survival model, based on separate survival models for men and women, with the weighting applied at baseline.

The EAG also notes that the company has used life tables for the UK. The EAG believes that it would be more appropriate to use life tables for England.

(b) Errors related to costs of treatment and disease management, including AEs

(b-i) Exclusion of costs of treatment administration/monitoring and drug acquisition for some modelled pathways

As described in Table 23, the company had intended to apply the following treatment pathway in the model:

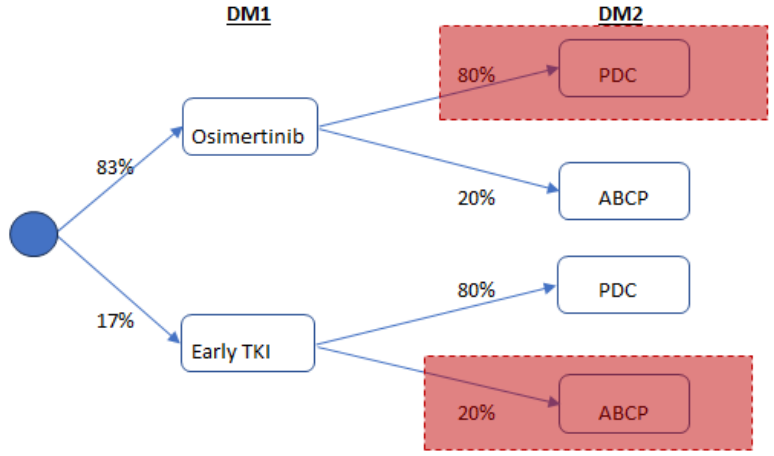
1. In the active monitoring group, 83% of patients receive osimertinib and 17% receive an early TKI in DM1, and of those who relapse, 80% receive PDC and 20% receive ABCP in DM2.
2. In the adjuvant osimertinib group, prior to the 48-month re-treatment timepoint, all patients receive PDC in DM1 followed by docetaxel in DM2.
3. In the adjuvant osimertinib group, after the 48-month re-treatment timepoint, 50% of patients receive osimertinib in DM1 followed by PDC or ABCP in DM2, and 50% receive PDC in DM1 followed by docetaxel in DM2.

The company's model includes several errors in attributing the costs to these pathways, as illustrated in Figure 38 and Figure 39:

- For patients receiving second-line treatment in the active monitoring group, the model calculations erroneously exclude treatment administration/monitoring and acquisition costs for PDC for the 80% of patients who were treated with osimertinib in DM1 (see Figure 38).

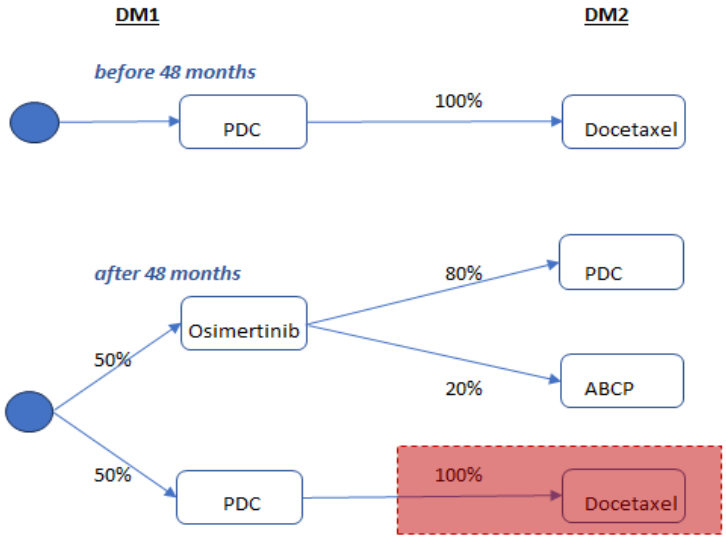
- For patients receiving second-line treatment in the active monitoring group, the model erroneously excludes treatment administration/monitoring and acquisition costs for patients receiving ABCP in those patients who were treated with an early TKI in DM1 (see Figure 38).
- In the adjuvant osimertinib group, the treatment administration/monitoring and acquisition costs of second-line docetaxel in DM2 are missing for 50% of the re-treated group (people who were treated with PDC in DM1 after 48 months) (see Figure 39).

Figure 38: Subsequent treatment pathways for distant metastases in the active monitoring arm (location of errors in drug administration/monitoring and acquisition costs highlighted in red)



Missing blocks for treatment administration/monitoring and acquisition costs are highlighted in red.

Figure 39: Subsequent treatment pathways for distant metastases in the adjuvant osimertinib arm (location of errors in drug administration/monitoring and acquisition costs highlighted in red)



Missing block for treatment administration/monitoring and acquisition costs is highlighted in red.

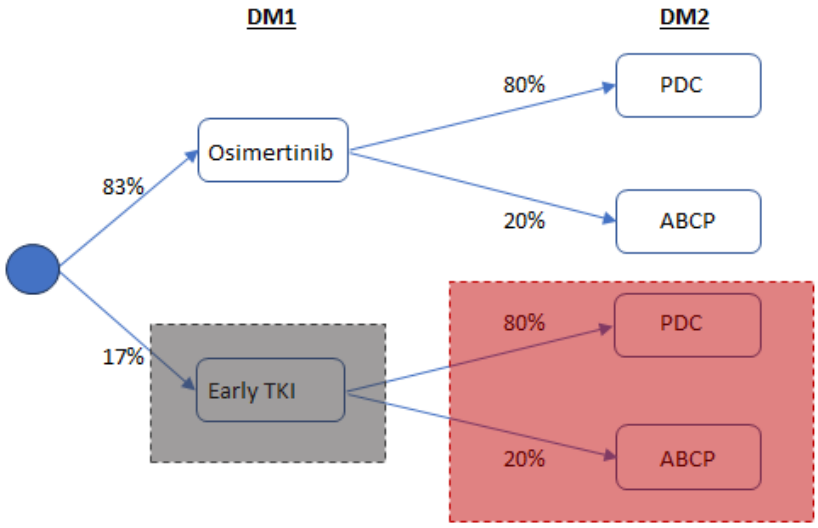
(b-ii) Exclusion of disease management costs for some patients in the model

The model erroneously excludes disease management costs for some patients in the active monitoring group, as shown in Figure 40:

- Disease management costs for DM2 are erroneously excluded for patients who receive an early TKI in DM1 and are subsequently treated with either PDC or ABCP in DM2.
- The one-off costs of treating CNS metastases (see Table 44) are not applied to early TKI-treated patients in DM1.

In addition, disease management costs for patients in the DF state are assumed to be zero after 4 years in both treatment groups. This leads to an inconsistency between the assumed time of discharge and the assumed final cure timepoints. Following the clarification round, the company amended the model to include disease management for uncured patients up to the final cure timepoints. However, the EAG considers this revised assumption to be inappropriate, as it is not possible for clinicians to determine which patients are cured or uncured (at least not until some assumed cure timepoint). Based on clinical advice, the EAG believes that these disease management costs should be applied in full until the assumed final cure timepoint in each group. The company's second updated version of the model included this as a scenario analysis (see Section 5.4).

Figure 40: Subsequent treatment pathways for distant metastases in the active monitoring arm (location of errors in disease management costs highlighted in red and grey)



Missing block for disease management costs in DM2 is highlighted in red.
Missing block for CNS management costs is highlighted in grey.

(b-iii) Incorrect treatment cycle duration used to estimate costs of carboplatin and paclitaxel (ABCP regimen)

The company's model calculations for ABCP assume that carboplatin and paclitaxel are given every 4 weeks. The EAG believes that these calculations should apply a 3-week cycle duration to reflect the ABCP dosing regimen in IMPower150.[40]

(b-iv) AE frequencies, management costs and disutilities

The calculations used to estimate total AE management costs and QALY losses erroneously exclude the frequency, cost and disutility associated with decreased ejection fraction. This error impacts on costs only as the disutility associated with this event is assumed to be zero (see Table 39).

(c) Discrepancy between the company's intended pathway and the pathway reflected in the executable model (re-treated sub-model, TP8)

All patients in the osimertinib group who experience distant relapse from 4 years after model entry transition to the same DM1 re-treatment sub-model and then the subsequent DM2 sub-model, regardless of whether they are re-treated with osimertinib or receive PDC in DM1. As described in CS Table 41 (and Figure 39 of this EAG report), the DM2 re-treated sub-model in the osimertinib group should consist of three groups of patients: (i) osimertinib-retreated patients who receive PDC in DM2, (ii) osimertinib-retreated patients who receive ABCP in DM2, and (iii) PDC-treated patients who receive docetaxel in DM2. The company estimated TP8 using a weighted survival model comprising 80% of a survival model fitted to the erlotinib/gefitinib arm of FLAURA and 20% of a survival model fitted to the ABCP arm of IMPower150, which represents 80% of PDC-treated patients and 20% of ABCP-treated patients, respectively. However, this approach does not account for the company's intended assumption that the 50% of patients who are not re-treated with osimertinib after 4 years would receive docetaxel in DM2 (following PDC in DM1).

(d) Apparent discrepancy in coefficients of some parametric survival models used to inform TP8 (DM2 to dead)

Within the company's executable model (worksheet "Transitions"), the parameters of the log-logistic, log-normal, Gompertz and generalised gamma survival models for TP8 are the same for both the osimertinib and TKI arm groups of FLAURA.[39] This appears to be a copy/paste error. However, these models were not selected for inclusion in the company's base case analysis; hence, the ICER remains unaffected.

(e) Unequal increments in the proportion of cured patients between consecutive cycles during the warm-up period

The model applies a warm-up period of 12 months in the active monitoring group, and 48 months in the adjuvant osimertinib group. The EAG believes that the company had intended for the proportion of patients cured during this period to increase linearly between consecutive model cycles. However, this is not the case - the increase in the cured proportion in the last cycle before reaching 95% cure is higher than the increase between all other previous cycles. This error can be seen in Figure 11.

(f) The sum of alive and dead patients in the osimertinib arm does not sum to 1.0

The model trace includes a set of calculations which are intended to check whether the number of patients in the alive and dead model states sums to 1.0. This condition is satisfied in the active monitoring group, but there are minor discrepancies at all timepoints in the adjuvant osimertinib group. Given the complexity of the model implementation, the presence of this issue is unsurprising. The EAG notes that this error is unlikely to have a meaningful impact on the ICER.

The company's clarification response[42] (questions C17, C20-C24, C27-C28) acknowledges that issues (a), (b-i) except the docetaxel cost issues, (b-ii),(b-iv),(d),(e), and (f) were errors. These issues were resolved in an updated version of the company's model provided as part of their clarification response. The results of this updated model are summarised separately in Section 5.4. The correction of these errors results in a small reduction in the company's base case ICER.

(2) Exclusion of adjuvant chemotherapy as a comparator for adjuvant osimertinib

The final scope for TA761[20] included a single comparator - established clinical management without adjuvant osimertinib (active monitoring). The final scope[33] for the current appraisal includes two comparators: (i) established clinical management without adjuvant osimertinib (active monitoring) and (ii) platinum-based (adjuvant) chemotherapy. The company's economic model includes a comparison between adjuvant osimertinib and active monitoring, but does not include a comparison between adjuvant osimertinib and adjuvant chemotherapy. The company's description of the current post-surgical treatment pathway in Section B.1.3.3.2 of the CS[2] also mentions the use of neoadjuvant treatment with nivolumab plus chemotherapy in patients without EGFR and ALK mutations, and the use of adjuvant atezolizumab in patients with high PD-L1 disease. The CS explains that these immunotherapy options are not relevant comparators for adjuvant osimertinib and they are not included as comparators in either the NICE scope or the company's economic model.

As noted in Section 3.3, the CS[2] argues that adjuvant chemotherapy is not a relevant comparator for this appraisal. The company presents several arguments in support of this view:

- Adjuvant osimertinib is not intended to displace chemotherapy as it provides an additional option for further adjuvant therapy after the patient/clinician decision to receive/administer adjuvant chemotherapy.
- Patients who were enrolled in ADAURA[36] were randomised after the option to receive adjuvant chemotherapy following complete resection; hence, outcomes were measured from randomisation, not from the initiation of first adjuvant therapy. Comparing outcomes for therapies given at different points in the treatment pathway would inappropriately introduce a selection bias.
- Prior chemotherapy use was not a stratification factor in ADAURA and subgroups defined by prior adjuvant chemotherapy were not adequately powered.

- There is no available evidence that would permit a robust comparison between adjuvant osimertinib and adjuvant chemotherapy.
- Adjuvant chemotherapy was not included as a comparator in TA761[20] and there is no clear rationale for deviating from the scope of this earlier appraisal.

The EAG notes that in ADAURA,[36] approximately 60% of patients had received prior chemotherapy, whereas the SACT data (summarised in CS Appendix R[37]) suggest that only around 27% of patients treated with adjuvant osimertinib via the CDF had received prior adjuvant chemotherapy. The stage distributions in the ADAURA and the SACT populations appear to be broadly similar. Other things being equal, the comparison of these data might suggest that some adjuvant chemotherapy use has been displaced through patients receiving adjuvant osimertinib directly after complete resection without first receiving adjuvant chemotherapy. During the clarification round, the EAG asked the company to comment on whether adjuvant osimertinib might have displaced adjuvant chemotherapy, and whether data exist to inform an ITC between these options (see clarification response,[42] question B1). The company's response states that there is paucity of evidence regarding the use of adjuvant chemotherapy in the population of interest in UK clinical practice prior to the introduction of adjuvant osimertinib and argues that *"the suggestion that adjuvant chemotherapy is being displaced by adjuvant osimertinib cannot be substantiated."* The company's clarification response also reiterates several of the arguments detailed in the bullet points above. The company's response does not mention any potential evidence sources that could inform an ITC.

The EAG sought further advice from their clinical advisors regarding relevant comparators for adjuvant osimertinib. Their comments are summarised below:

- Both clinical advisors agreed that neoadjuvant nivolumab is not a relevant comparator because this treatment is offered only to patients who do not have EGFR mutations. The EAG therefore agrees that neoadjuvant nivolumab is not a relevant comparator.
- Both clinical advisors commented that adjuvant atezolizumab is restricted for use in patients with PD-L1 ≥50%, but noted that there are some patients who have both PD-L1 high disease and EGFR mutations. In these circumstances, the clinical advisors stated that they would treat the EGFR mutation first, because this is what drives the disease. The EAG agrees that adjuvant atezolizumab is not a relevant comparator.
- The clinical advisors commented that adjuvant treatment planning would typically occur at a single decision point, rather than as a series of sequential decisions. Because patients who have undergone complete resection do not have measurable disease, clinicians would not wait until the patient has completed adjuvant chemotherapy before deciding whether to offer adjuvant osimertinib.

- With respect to the use of adjuvant chemotherapy, one clinical advisor stated that in their clinical practice, they had not offered patients treatment with adjuvant chemotherapy and then subsequently offered adjuvant osimertinib. They stated that this was partly because the patients that they had offered adjuvant osimertinib to tended to have very early-stage disease (typically stage IB), but was also due to the limited absolute benefit and additional burden of chemotherapy-related toxicity. They stated that if they had a patient with higher stage disease (e.g., stage IIIA), they would consider offering adjuvant chemotherapy prior to osimertinib if needed, but that their general preference was to get patients onto adjuvant osimertinib as soon as possible following surgery, without the use of prior adjuvant chemotherapy. The clinical advisor was unsure whether this treatment approach was also reflective of broader NHS practice.
- The EAG's second clinical advisor did not believe that adjuvant chemotherapy was a relevant comparator and commented that the low rate of adjuvant chemotherapy use in SACT most likely reflected the use of adjuvant osimertinib in a population who would be less likely to be suitable for adjuvant chemotherapy.

Overall, the EAG believes that it is reasonable to exclude chemotherapy as a comparator for this appraisal. The EAG also agrees with the company that performing an ITC between these options would likely introduce a selection bias between the treatment groups due to the differing points in the pathway at which adjuvant chemotherapy and adjuvant osimertinib are given.

(3) Uncertainty around long-term DFS and OS outcomes for adjuvant osimertinib, including potential curative effects

During TA761,[20] the Appraisal Committee highlighted concerns around the immaturity of the DFS data (based on the January 2020 DCO), and noted uncertainty around the extent to which a benefit in DFS would translate into a benefit in OS. The TA761 guidance highlighted the Appraisal Committee's concerns that adjuvant osimertinib may only delay rather than prevent disease recurrence, as well as uncertainty around the plausibility of the 5-year cure timepoint applied in both groups of the company's previous economic model (see Box 1).

As discussed in Section 4.2, more recent DCOs for DFS and OS are available from ADAURA[36] for the current appraisal. The updated results suggest that adjuvant osimertinib leads to a statistically significant benefit over placebo, both in terms of DFS (HR 0.27, 95% CI 0.21 to 0.34, p=NR; DCO 11th April 2022) and OS (HR 0.49, 0.34 to 0.70, p<0.0001; DCO 27th January 2023). This updated evidence suggests that adjuvant osimertinib reduces the risk of distant recurrence and death in patients with stage IB-IIIA EGFRm NSCLC. However, the maximum follow-up in ADAURA remains limited which means that there is uncertainty about longer-term outcomes in both treatment groups.

The CS[2] indicates that cure is expected in a proportion of patients receiving either active monitoring or adjuvant osimertinib. However, the CS also generally acknowledges that despite the availability of more recent DCOs from ADAURA,[36] the evidence to support an assumption of cure from this trial is limited, particularly with respect to the adjuvant osimertinib group. In particular, Section B.2.6.1.1 of the CS comments that the DFS curve for placebo in ADAURA is beginning to reach a plateau by approximately 48 months, but that the interpretation of the DFS curve for the osimertinib group is limited due to censoring and the low number of patients at risk (see Figure 2). Whilst it is not clearly evident from the Kaplan-Meier plot for DFS, the company asserts that the osimertinib curve is also expected to reach a plateau.

The company has also provided additional information in support of an assumption of cure in both treatment groups. In response to a request for clarification from the EAG (see clarification response,[42] question B3), the company explained that it is well-established that surgical resection for early-stage NSCLC patients has curative potential, that most disease recurrences (without osimertinib) occur within 18-24 months of complete resection, and that the clinical experts consulted by the company confirmed that it is reasonable to assume cure by 5 years in patients who are receiving active monitoring alone. The company's clarification response further states that whilst the clinical experts consulted by the company in 2023 were in agreement that a proportion of patients receiving adjuvant osimertinib would also be expected to achieve cure, there was some disagreement about when cure should be assumed to apply, with 2 of 5 clinicians stating that a cure timepoint of 5 years should be assumed, and 3 of 5 clinicians stating that the additional time on treatment with osimertinib should be accounted for in determining the cure timepoint.[7] In TA761,[20] the Appraisal Committee considered analyses conducted by the company and the EAG which assumed a cure timepoint of 5 years in both groups, as well as a pessimistic ERG scenario which assumed cure at 5 years for active monitoring and 8 years for adjuvant osimertinib. The company's current model applies the same final cure timepoints as the ERG's pessimistic scenario, but also includes a preceding warm-up period in both groups starting at the end of year 4. The EAG notes that the maximum follow-up time in the latest DFS data-cut from ADAURA is approximately 6 years, which is shorter than the company's assumed final cure timepoint in the adjuvant osimertinib group of the economic model (8 years).

The company's model suggests that compared with active monitoring, adjuvant osimertinib leads to an incremental benefit in both DFS and OS. This is evident from the sustained gap between the modelled DFS and OS functions for the treatment groups, as shown in Figure 31 and Figure 32, respectively. The magnitude of this gap, and the duration over which it is maintained, is a function of the clinical data from ADAURA and external data, as well as the company's cure assumptions. The EAG believes that these cure assumptions, and their influence on the gap in DFS and OS between the treatment groups, reflect the key area of uncertainty for the current appraisal.

EAG comments on uncertainty around expected benefits in DFS and OS

(a) Availability of updated data from ADAURA

Whilst additional data on DFS have become available since TA761,[20] the EAG notes that the updated data-cut is not particularly recent - at the time of writing, the latest data-cut of DFS from ADAURA[36] is nearly 2 years old. The EAG understands that the study has been unblinded and no further data on recurrence are being collected. This is unfortunate, as an extra 12 months of data from ADAURA might have provided valuable information about whether the gap in observed DFS is likely to persist in the longer-term. The latest DCO for OS is more recent than that for DFS (including observations up to a maximum follow-up time of around 7 years). However, these data are subject to high levels of censoring.

[redacted]

(b) Observed versus modelled hazards

During the clarification round, the EAG asked the company to provide plots of the time-varying HRs for DFS and OS for osimertinib versus placebo in ADAURA,[36] based on the latest DCOs for each endpoint (see clarification response,[42] question C4). The EAG requested these additional analyses because they would have allowed for an exploration of trends in the relative treatment effect over the observed period of the trial (i.e., whether the effect is constant, increasing or diminishing over time). This could have provided some basis for informing assumptions about what might be expected to happen to the relative treatment effect during the extrapolation period of the model. In addition, an analysis of the observed and model-predicted hazard functions for DFS could have been used to determine whether the model predictions are consistent with the observed data from ADAURA.

In response to the EAG's request, the company stated that the interpretation of the DFS data beyond 48 months is limited due to high levels of censoring in the adjuvant osimertinib group and low numbers of patients at risk in the placebo group, and that the *"latter period of a piecewise hazard ratio analysis for DFS would be highly uncertain, and given the censoring in the osimertinib arm, overly conservative."* The company's response further states that this analysis was not pre-specified in the statistical analysis plan (SAP) and that it was not considered appropriate as a *post hoc* analysis for DFS or OS from ADAURA.[36] The company did not provide the analysis requested by the EAG. The EAG acknowledges some of the limitations raised by the company, but maintains that undertaking an exploratory analysis of the time-varying HR could have been useful for informing the model assumptions, regardless of whether it had been pre-specified in a SAP.

As the company did not provide the requested analyses, the EAG conducted them instead. The EAG's analyses focussed on DFS rather than OS, because the DFS data are more mature and this endpoint reflects the part of the economic model to which the cure assumptions are applied. The EAG replicated the pseudo-IPD for DFS for each treatment group in ADAURA using the algorithm reported by Guyot *et al.*[87] The EAG then generated plots of the empirical and smoothed hazard functions for DFS in each treatment group (see Figure 41) and a plot of the time-varying HR for osimertinib versus placebo using the April 2022 DCO of DFS in ADAURA (see Figure 42). These analyses were conducted using the *muhaz* package in R. The EAG also generated plots of the aggregate DFS hazards using the company's economic model to assess whether the model predictions are consistent with the observed data from ADAURA.

The empirical hazard functions from ADAURA (Figure 41) indicate that the risk of relapsing or dying in the placebo group is decreasing over time, and drops to a very low absolute hazard by 5 years; this pattern is generally consistent with the company's assumption of cure by this timepoint. Conversely, the absolute DFS hazard in the adjuvant osimertinib group is increasing over time. Unsurprisingly, the time-varying HR (Figure 42) indicates that the relative treatment effect on DFS is worsening over time. The predicted DFS hazards for both treatment groups in the company's economic model are broadly consistent with the hazards observed within the first 4 years of ADAURA,[36] but the model-predicted hazard in the adjuvant osimertinib group features a noticeable turning point after around 4 years, which ultimately leads to a very low absolute hazard by 8 years (see dashed red line in Figure 43). This turning point is driven by the company's cure assumptions and is not consistent with what has been observed in ADAURA. The EAG notes that whilst it is possible that further follow-up in ADAURA might lead to a turning point in the hazard for the osimertinib group, this trend has not yet been observed in the available data, despite follow-up out to around 6 years.

Figure 41: Smoothed and empirical hazards for DFS in ADAURA, adjuvant osimertinib and active monitoring groups

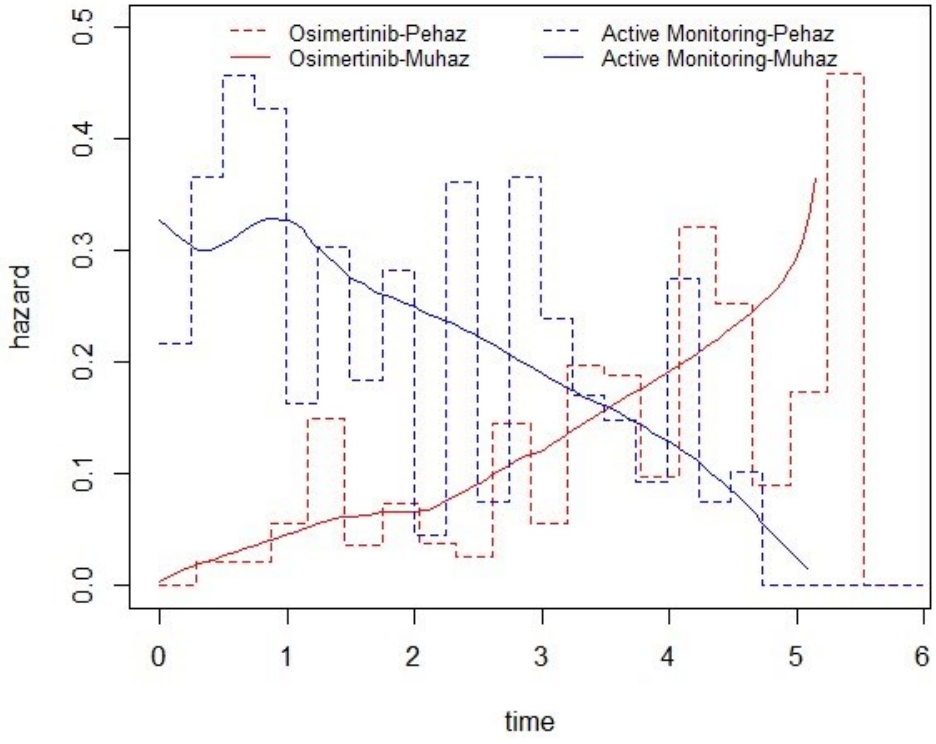


Figure 42: Smoothed and empirical time-varying hazard ratio plots in ADAURA, adjuvant osimertinib group versus active monitoring group

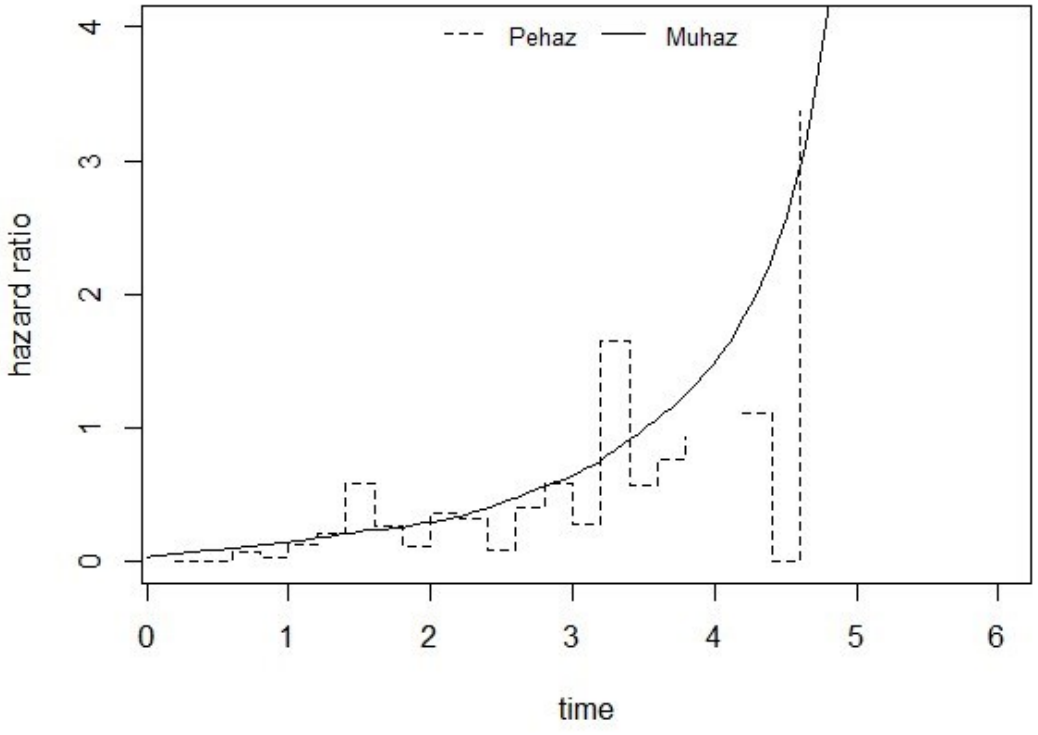
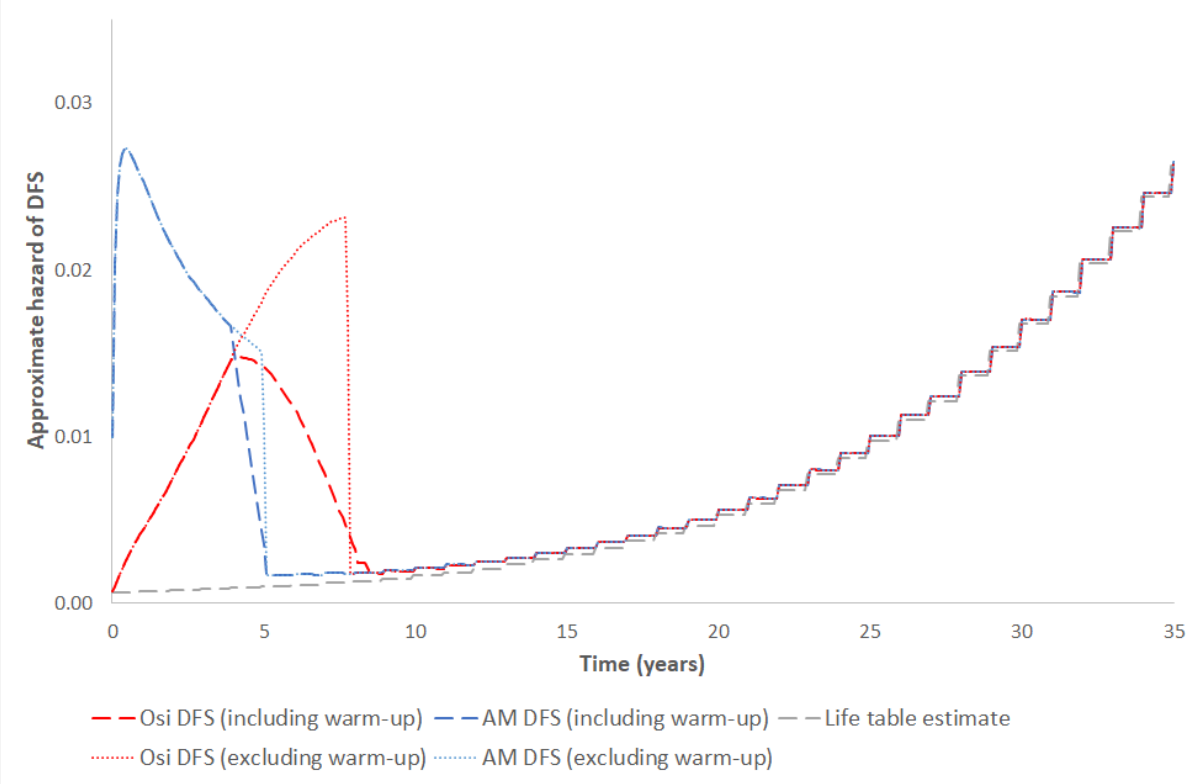


Figure 43: Company's model-predicted DFS hazards



Osi - osimertinib; AM - active monitoring; DFS - disease-free survival
Notes: The company's economic model applies a cure assumption to patients receiving active monitoring starting at 0% at the end of year 4, increasing almost linearly to 95% by the end of year 5. The company's model applies a cure assumption to patients receiving adjuvant osimertinib starting at 0% at the end of year 4, increasing almost linearly to 95% by the end of year 8.

(c) Statistical modelling of cure

The TA761 guidance document[20] stated that when the guidance is reviewed, the company should consider using formal statistical modelling of cure (for example, using an MCM; see Box 1). The CS[2] describes the use of MCMs fitted to the ANITA trial[86] to support the modelled cure assumptions for patients receiving active monitoring. However, the CS does not describe the application of MCMs fitted to DFS or OS data from ADAURA.[36] During the clarification round for the current appraisal, the EAG asked the company to fit MCMs to the available data on DFS and OS for each treatment group in ADAURA (see clarification response,[42] question C6). The EAG requested these additional analyses because they were suggested in the TA761 guidance document, and because they might have been useful for determining whether MCMs fitted to the ADAURA data could generate cure fractions, and, if so, whether those cure fractions were consistent between alternative MCMs. This might have provided supportive evidence for assuming cure in both treatment groups.

In their clarification response,[42] the company stated that owing to insufficient follow-up, the limited sample size, as well as the company's assumed cure timepoints of 5 and 8 years for active monitoring and adjuvant osimertinib, respectively, the DFS data from ADAURA[36] are not sufficiently mature to

robustly fit MCMs. The company's clarification response stated that fitting such models would result in unreliable cure estimates, particularly for the adjuvant osimertinib group. The company did not provide the analysis requested by the EAG.

As the company did not provide the requested analyses, the EAG conducted them instead. The EAG fitted exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma MCMs to the pseudo-IPD on DFS from ADAURA[36] using the *flexsurvcure* package in R. The authors of this package warn that the generalised gamma and Gompertz distributions have issues with convergence and numerical instability and so these models should be interpreted with caution. Table 50 summarises the AIC/BIC statistics for each MCM. Table 51 summarises the cure fractions estimated for each MCM. Figure 44 presents the MCM survival distributions for the adjuvant osimertinib group. Figure 45 presents the MCM survival distributions for the placebo group.

The EAG was able to fit MCMs to the data for both groups of ADAURA.[36] Within the active monitoring group, all MCMs except for the generalised gamma distribution produced broadly consistent cure fractions ranging from 23% to 32%. Within the adjuvant osimertinib group, whilst all models converged, only the Gompertz MCM and generalised gamma MCM were able to generate cure fractions. Based on the findings of this survival modelling exercise, the EAG believes that the ADAURA data provide some supportive evidence of cure for patients receiving active monitoring. Whilst cure might become more apparent for the osimertinib group with additional follow-up in ADAURA, the EAG's MCM fitting exercise suggests that currently there is not strong supportive evidence of cure in this group within the available DFS data. However, as noted above, no further data-cuts of DFS are expected.

Table 50: AIC and BIC statistics – MCMs fitted to ADAURA DFS data

Model	**Adjuvant osimertinib**		**Placebo**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential MCM	663.08	670.73	978.15	985.83
Weibull MCM	**624.22**	**635.69**	971.5	983.01
Gompertz MCM	627.26	638.74	979.09	990.6
Log-normal MCM	628.24	639.71	956.44	967.95
Log-logistic MCM	625.62	637.1	963.35	974.87
Gamma MCM	625.02	636.5	967.96	979.47
Generalised gamma MCM	625.69	640.99	**955.94**	**971.29**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; MCM - mixture-cure model
Best fitting model shown in bold

Table 51: Estimated cure fractions – MCMs fitted to ADAURA DFS data (95% CIs shown in parentheses)

Model	Adjuvant osimertinib	Placebo
Exponential MCM	0% (0%, 100%)	26% (18%, 35%)
Weibull MCM	0% (0%, 100%)	32% (26%, 39%)
Gompertz MCM	41% (11%, 80%)	31% (24%, 40%)
Log-normal MCM	0% (0%, 100%)	23% (14%, 36%)
Log-logistic MCM	0% (0%, 100%)	24% (16%, 34%)
Gamma MCM	0% (0%, 100%)	32% (26%, 38%)
Generalised gamma MCM	24% (0%, 100%)	1% (0, 100%)

MCM - mixture-cure model

Figure 44: Observed and MCM-predicted DFS, ADAURA, adjuvant osimertinib group

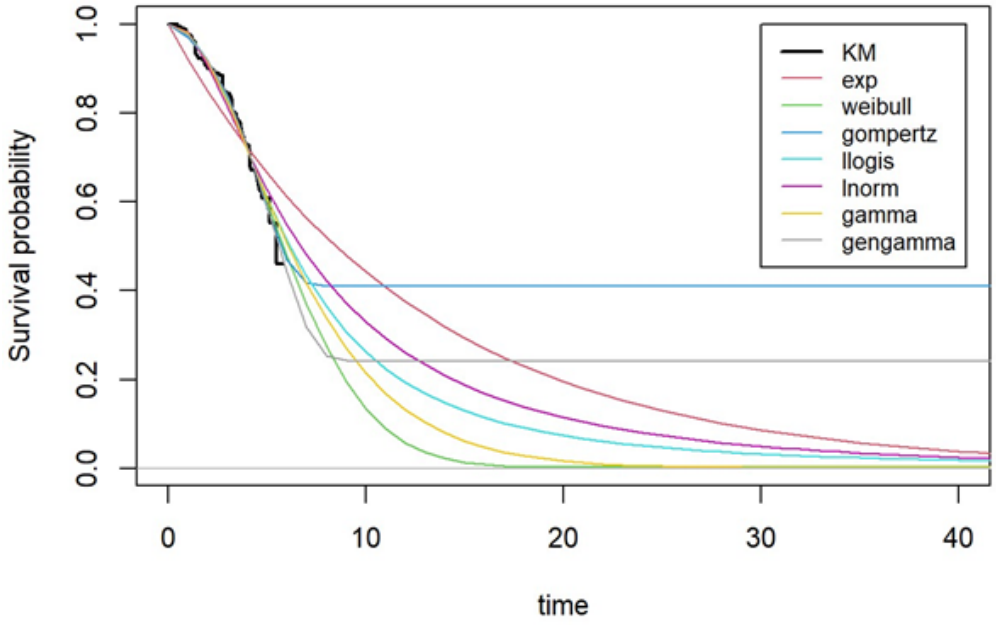
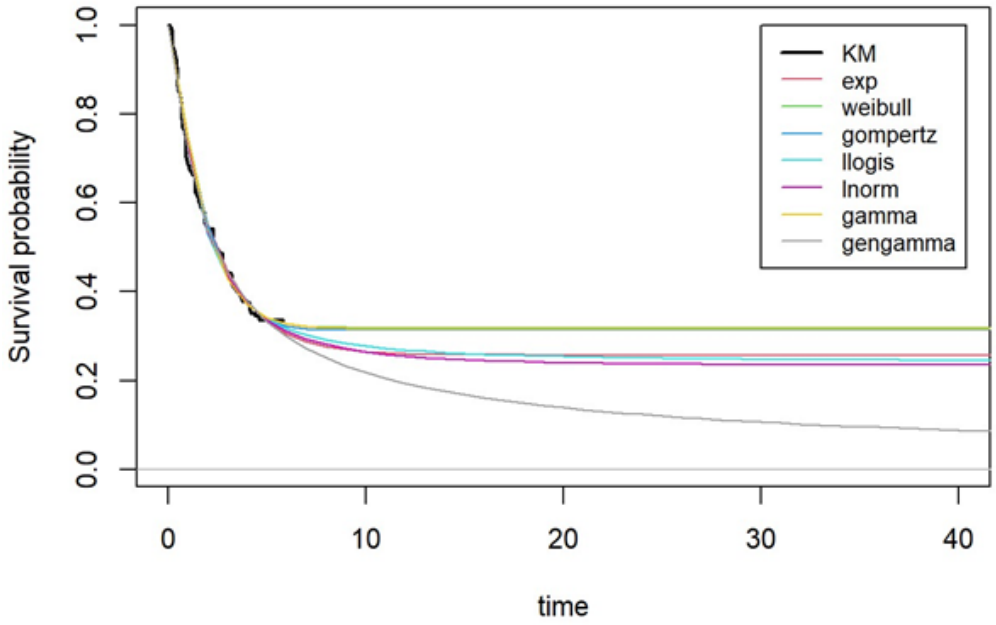


Figure 45: Observed and MCM-predicted DFS, ADAURA, placebo group



(d) EAG clinical advisors' expectations of cure with and without adjuvant osimertinib

The EAG's clinical advisors agreed that osimertinib is an effective adjuvant therapy. However, they highlighted uncertainty around the magnitude and expected duration of the gap in DFS and OS:

- The first clinical advisor commented that they supported an 8-year cure assumption on the basis that *"the clock for achieving cure starts when active treatment is stopped."* Therefore, for patients completing three years of treatment with adjuvant osimertinib, an 8-year cure assumption would seem reasonable. They considered that the company's model-predicted gap in DFS and OS was clinically plausible, but that there remained considerable uncertainty regarding the longer-term DFS and OS after completing 3 years of adjuvant treatment with osimertinib.
- The second clinical advisor was unsure whether the gap in DFS and OS would be maintained. They stated that it was plausible that there may be a sustained gap which is smaller than that predicted by the company's model. However, they also mentioned the possibility that the osimertinib DFS function might catch up with the placebo DFS function (i.e., that there would be no sustained gap in the longer-term).

EAG's conclusions regarding long-term outcomes for adjuvant osimertinib and active monitoring

Based on the information and analyses presented above, the EAG notes the following points:

- Despite the collection of additional data since TA761,[20] there remains considerable uncertainty around the long-term benefits of adjuvant osimertinib on both DFS and OS.
- The EAG's analyses of time-varying hazards indicate that the DFS hazard for the placebo group becomes very low within the observed period of ADAURA, which provides some support for a cure assumption for active monitoring prior to this timepoint.
- The DFS hazard in the adjuvant osimertinib group increases over the observed period of ADAURA. This does not provide supportive evidence for a cure assumption within the 6-year maximum follow-up period of the trial. The warm-up period in the company's economic model leads to a turning point in the absolute hazard which is inconsistent with the hazard in the observed period of ADAURA. The EAG does not believe there is a strong rationale for including a turning point in DFS in the osimertinib group within the first 6 years of the model.
- The EAG's fitted MCMs provide some support for the company's cure assumptions in the active monitoring group, but not in the adjuvant osimertinib group. This does not mean that adjuvant osimertinib is not curative, but it does suggest that the available data from ADAURA are not sufficiently mature to provide evidence to support this assumption.
- One of the EAG's clinical advisors considered the company's projected DFS and OS to be clinically plausible but uncertain, whereas the other advisor was unsure whether the gaps in DFS and OS would be maintained in the longer-term.

Exploring the impact of uncertainty around long-term DFS, OS and cure assumptions on the ICER for adjuvant osimertinib forms the main focus of the EAG's exploratory analyses (see Section 5.5).

(4) Issues relating to the company's survival analysis

The EAG has several concerns regarding the company's survival analysis presented in the CS.[2] These concerns are discussed below based on the general considerations around model fitting and selection set out in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[95, 96]

(a) Consideration of suitability of joint models

The company generated log cumulative hazard plots for each dataset modelled and used these together with plots of the Schoenfeld residuals to assess the appropriateness of assuming PH. The company did not investigate the appropriateness of jointly fitted accelerated failure time (AFT) models. The company found evidence against PH in some cases and, for the sake of consistency, fitted separate models to the data for each treatment arm for all events, thereby avoiding the PH assumption. The EAG considers that fitting separate models is a reasonable approach which does not require strong assumptions regarding an observed treatment effect between trial arms being maintained beyond the observed period of the data.

(b) Range of candidate models assessed

The company fitted six standard parametric survival distributions to data relating to each transition, including exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma models. Based on visual inspection, the EAG notes that none of the standard parametric models provide a good fit to the data for the osimertinib group for TP1 (Figure 13). The empirical hazard of TP1 for osimertinib (Figure 12) has two turning points, but the six fitted standard parametric distributions can allow for one turning point at most, which means that the included parametric models cannot adequately represent the observed data. Similarly, none of the models provide a good representation of the hazards of TP2 for placebo (Figure 15).

During the clarification round, the EAG asked the company to explore fitting RCS models to the data for TP1 and TP2 (see clarification response,[42] question C10). However, the company did not fit these models. The company's response states: "*splines were not considered appropriate given that standard models provided a sufficiently good fit to the data.*" The EAG maintains its view that the use of more flexible methods may better reflect the underlying hazards and Kaplan-Meier estimates for these transitions.

(c) Statistical and visual goodness-of-fit

Amongst other factors, the company's model selection process included consideration of statistical goodness-of-fit (AIC and BIC) and visual inspection. The EAG notes that the AIC/BIC values presented

in the CS[2] for TP1, TP2 and TP8 differ from the values included in the company's model. Following the clarification round, the company confirmed that the values reported in the CS are correct for TP1 and TP8, and corrected values were provided for TP2 osimertinib (see Table 28).

The EAG also notes some confusion about the role of AIC and BIC statistics. The CS cites Williams *et al*.,[84] stating that AIC statistics are not meaningful when competing risks are present. However, the company has used AIC to inform model selection. The EAG is unsure whether the company's use of AIC to inform model selection is appropriate.

(d) Consideration of the nature of hazards

The company presented the empirical and modelled hazard plots for TP1 and TP2 and considered the nature of hazards in the parametric survival model selection process in the CS.[2] However, the company did not present the empirical or modelled hazard plots for TP4, TP6, TP7 or TP8 in the CS. These plots were later provided as part of the company's clarification response[42] (question C3), but these were not used by the company to select their preferred parametric survival models.

As part of the company's clarification response[42] (question C5), for TP1 osimertinib, the company states *that "the Weibull, loglogistic, and Gompertz modelled hazards were predicting increasing hazards overtime and considered to be overly influenced by the tail of the curve which has higher censoring and lower number of people at risk."* The EAG acknowledges the uncertainty in the tail of the curve, but disagrees with the exclusion of the Weibull, log-logistic, and Gompertz distributions, as the predicted hazard plots from these three models align better with the empirical hazard plots, compared with the log-normal, generalised gamma and exponential models. In particular, the company's selected base-case log-normal model predicts a slowly decreasing hazard, which contradicts the trend within the empirical hazards.

Similarly, for TP2 osimertinib, the company's clarification response[42] also states that "*the Weibull and Gompertz models were predicting sharply increasing hazards overtime [sic] and considered to be overly influenced by the tail of the curve which has higher censoring and lower number of people at risk."* The EAG acknowledges the uncertainty in the tail of the curve, but considers that the predicted hazard plots from the Weibull and Gompertz models appear to provide a better fit to the empirical hazard plot, compared to the company's base case log-logistic distribution.

The EAG also notes the following limitations regarding the company's preferred survival models for TP6 osimertinib, TP7 and TP8 IMPower150. For TP6 osimertinib, the empirical hazard plot has a decreasing trend from around 18 months until 48 months (the maximum follow-up period shown in the plot), but the selected Weibull model predicts a slightly increasing trend. For TP7, the empirical hazard

plot has a decreasing trend, but the selected exponential model has a constant hazard. For TP8 IMPower150, the empirical hazard and model-predicted hazard plots are not presented in the CS[2] or the company's clarification response.[42]

The EAG believes that the hazards in TP1 osimertinib and TP2 osimertinib may be represented better by choosing a different survival model. Alternative models are considered within the EAG's exploratory analyses.

(e) Assessment of extrapolations

The plausibility of the survival model extrapolations is a key element of model selection and the company gave considerable weight to this factor. In particular, the EAG notes that with respect to model selection for TP1 osimertinib and TP2 osimertinib, the company considered pessimistic models to be clinically implausible given the expectations of cure. This is incongruous for several reasons:

(i) None of the standard parametric models considered by the company appear to suggest that the osimertinib is curative, including the company's selected base case models;
(ii) The cure assumptions themselves, including the cure time point and the cure fraction, are uncertain;
(iii) The EAG considers that selecting a parametric survival model which is intended to be compatible with cure and then applying a structural assumption of cure on that model may be accounting for the cure twice; and
(iv) The extrapolations beyond the 4-year timepoint for many of the parametric survival models (except the Gompertz distribution in TP1 and the exponential, Gompertz and log-normal distributions in TP2) have a limited impact on the economic model predictions, as the cure assumptions (including the warm-up period) override the probabilities predicted by the parametric survival model. Within the economic model, the hazard applied in each treatment group after the final 8-year cure timepoint is low (5% of the model-predicted hazard).

EAG conclusions on the company's survival analysis

Notwithstanding the EAG's concerns regarding the restricted range of candidate models, the EAG believes that in the company's model selection process: (i) cure should not have been considered within the assessment of extrapolations; (ii) the nature of the modelled hazard should have been given more weight; and (iii) the fit of the aggregated DFS and OS from the economic model to the observed DFS and OS should have also been given more weight, following the recommendations by Williams *et al.*[84] (although the EAG notes that is unclear whether this latter suggestion would have fully resolved the poor fit of the model to the aggregate OS data).

More flexible model forms (e.g., RCS distributions) would likely have better reflected the empirical hazards for TP1 and TP2; however, these have not been fitted by the company.

(5) Unconventional approach to modelling cure

The EAG believes that the company's approach to modelling cure is unconventional and that it features several arbitrary assumptions. Generally speaking, cure tends to be incorporated into health economic models using one of two approaches: (i) by fitting MCMs, which involve estimating cure fractions to determine the proportion of the population who are cured and who will not progress from or die as a consequence of their disease, or (ii) by applying a structural assumption of cure, whereby beyond some timepoint t_n, progression/mortality risk is assumed to be equivalent (or similar) to that of the general population.

The company's model borrows elements of each of these two approaches in its cure assumptions:

- It assumes that beyond the final cure timepoint of 5 years for active monitoring and 8 years for adjuvant osimertinib, the risk of experiencing loco-regional or distant relapse is very low (5% of the predicted probabilities estimated from the fitted parametric survival models for TP1 and TP2). This is similar to applying a structural assumption of a cure timepoint.
- It assumes that there are some patients who will not be cured. This is similar to an MCM, except that the company's approach assumes a single homogeneous population with lower risks applied to all non-relapsed patients after the cure timepoint, rather than modelling distinct subgroups of cured and uncured patients who are subject to different risks of relapse.
- Distinct from both the MCM and structural cure approaches, the company's model includes a warm-up phase in each treatment group, whereby the predicted risk of relapse estimated from the parametric survival models decreases approximately linearly in each successive model cycle after the end of year 4 until the final cure timepoint is reached.

The first two components of this approach, and the timepoints at which structural cure is assumed, were applied in the ERG's pessimistic scenario in TA761.[20] The inclusion of a warm-up period is a distinct feature of the company's model for the current appraisal which was not included in the company's previous model.

According to the CS[2] (page 88), the warm-up period was applied because clinical experts consulted by the company believed that the application of a warm-up period was more plausible rather than assuming an immediate cure timepoint from 5 years. The company's clarification response[42] (question C12) states that the company does not consider the cure approach to be unconventional and that *"this was the same approach that was presented and accepted in TA761."* The EAG disagrees, as the model used to inform TA761 did not include a warm-up period. In their clarification response, the company highlighted that there is precedent for this approach, as the model used to inform TA632 (trastuzumab emtansine for adjuvant treatment of human epidermal growth factor receptor 2 [HER2) positive early breast cancer)[97] also included cure timepoints applied to <100% of patients, with a preceding warm-up period in which

the cured proportion increases linearly. The company's response states that this approach was accepted in TA632. The EAG notes that the final guidance document for TA632 does not explicitly mention the model cure assumptions; however, ERG report for this appraisal highlighted uncertainty around this aspect of the company's model. Owing to the absence of alternative "better informed" evidence for these cure assumptions, the ERG accepted them, but tested them in sensitivity analyses. Within this earlier appraisal, the same cure assumptions were applied in both treatment groups, which led to a minimal impact on the ICER. In contrast, in the company's model for the current appraisal, the cure assumptions are not applied equally between the treatment groups, and these have a substantial impact on the ICER for adjuvant osimertinib.

In the current appraisal, the EAG does not believe that there is a strong rationale to determine the 4-year starting point for the warm-up period, or for the assumed linearly increasing proportion of patients being cured in each model cycle. As illustrated in Figure 41 and Figure 43, these assumptions introduce an inconsistency between the DFS hazards assumed in the model and the DFS hazards observed in ADAURA.[36] The EAG also notes that the assumptions regarding the warm-up period for the cure assumption have a substantial impact on the model-predicted DFS and OS, as well as on the ICER for adjuvant osimertinib. The impact of excluding the warm-up period is explored as a central part of the EAG's exploratory analyses.

(6) Uncertainty surrounding the use of osimertinib in the first-line metastatic setting (as re-treatment and for patients receiving active monitoring)

The TA761 guidance document[20] highlighted that re-treatment with osimertinib would be offered to some people with relapsed disease, but noted that the proportion of people having re-treatment with osimertinib was uncertain. The Appraisal Committee also highlighted uncertainty around the proportion of patients in the active monitoring group who would receive osimertinib as first-line treatment for metastatic disease.

(a) Re-treatment with osimertinib

The company's current model assumes that after 4 years since initiating adjuvant osimertinib, 50% of patients who experience distant relapse will be re-treated with osimertinib as first-line therapy for metastatic disease. Compared with the model used in TA761,[20] the re-treatment timepoint has been brought forward by 1 year (from 5 years to 4 years), but the re-treatment proportion of 50% remains unchanged between the previous and current versions of the company's model. The CS for the current appraisal[2] does not provide any additional information on the re-treatment proportion. The CS presents sensitivity analyses around the re-treatment timepoint, but not around the proportion of patients receiving re-treatment (see Table 47).

During the clarification process, the EAG asked the company why data on re-treatment were not collected in SACT, and whether any other data source, besides clinical opinion, could provide estimates of osimertinib re-treatment rates (see clarification response,[42] question C14). In their response, the company stated that during TA761, the Appraisal Committee concluded that SACT data collection was unlikely to provide meaningful data on the proportion of patients that would be re-treated with osimertinib in clinical practice in a reasonable timeframe, and noted that the assumed 50% re-treatment proportion was accepted by the Appraisal Committee and that this did not materially influence the ICER for adjuvant osimertinib. The company's response also states that within ADAURA,[36] [redacted] of patients in the adjuvant osimertinib arm who received a first post-study anti-cancer therapy received osimertinib as re-treatment, although this estimate was deemed immature and it was unclear whether these patients had previously progressed whilst receiving adjuvant osimertinib. The company's clarification response also states that real-world studies are expected to address re-treatment rates, but does not refer to or cite any specific study. As part of their response to clarification question C15, the company stated that none of the clinicians consulted by the company during the 2023 interviews *"had enough experience with the need to consider retreatment in practice."*

The EAG asked their clinical advisors about the proportion of patients who would be re-treated with osimertinib. The first clinical advisor stated that the *"vast majority"* of patients would be re-treated with osimertinib in the metastatic setting after four years of initiating adjuvant osimertinib. The second clinical advisor concurred with the first advisor's view, but noted that they would like to be able to offer re-treatment at an earlier timepoint if patients had discontinued before completing three years of adjuvant treatment.

The EAG notes that no new data have been presented on re-treatment rates for the current appraisal, and therefore this aspect of the company's model remains highly uncertain. The EAG also notes that whilst the re-treatment assumptions had little bearing on the company's base case ICER in TA761, this was because the cure timepoint coincided with the re-treatment timepoint (both occurring at 5 years). However, since the company has applied a later final cure timepoint in the current model, this means that assumptions about the re-treatment proportion will now have a greater effect on the ICER.

The EAG also notes that the company's model assumes that re-treatment with osimertinib is not associated with any loss of efficacy. The EAG's clinical advisors commented that this assumption is generally reasonable, although it is also plausible that re-treatment will lead to the development of earlier resistance and reduced efficacy in the metastatic setting.

(b) Use of osimertinib as first-line treatment following distant recurrence in the active monitoring group

The company's model assumes that 83% of patients receive osimertinib as a first-line treatment for metastatic disease in the active monitoring group (see Table 23). This proportion is based on 2023 Ipsos

market share data.[31] The EAG's clinical advisors commented that the proportion of patients receiving osimertinib would likely be higher than 83%. One of the EAG's clinical advisors commented that other early-generation TKIs, which are less effective and less toxic than osimertinib, would only be considered for those patients with a poorer PS, but that patients within the target population who experience distant recurrence tend to be fitter because they are identified early through active monitoring. The EAG notes that the Ipsos data reflect the overall population of patients with EGFRm NSCLC at first-line, rather than those who would specifically be fit enough to receive osimertinib (those with PS 0 or 1). Based on clinical advice, the EAG believes that the true proportion of patients who would receive first-line osimertinib may be higher than that assumed in the company's model.

(7) Use of external data from FLAURA and the need for calibration

In TA761,[20] the ERG and the Appraisal committee acknowledged that patients who are being actively monitored and who subsequently experience distant recurrence may have outcomes in advanced disease which are better than those seen in FLAURA.[39] This issue is discussed in Section B.3.3.4 of the CS for the current appraisal,[2] whereby the company notes that most (4 of 5) of the clinical advisors that they consulted stated that *"they would expect survival outcomes for ADAURA patients who progressed to metastatic disease to perform better than a newly diagnosed patient with stage IIIB/IV disease."* The EAG's clinical advisors also agreed with this majority view.

This issue impacts on model-predicted OS – without additional adjustment, the company's economic model generates estimates of predicted OS which do not provide a good representation of the observed OS data in ADAURA[36] (see dashed lines in Figure 32). In order to make the model-predicted OS consistent with the observed OS in ADAURA, the company included a calibration factor of [redacted] which is applied as an HR to part/all of the survival models used to estimate TP4, TP6 and TP8 (see footnotes to Table 25). This calibration approach forces the model-predicted OS to better align with the ADAURA OS. This issue was not evident in the earlier model used to inform TA761 because the ADAURA data were less mature. The EAG has some concerns regarding the company's calibration approach:

- The executable version of the company's economic model does not include the functionality to derive or to re-estimate the calibration factor. During the clarification process, the EAG asked the company to provide a version of the model which includes this functionality (see clarification response,[42] question C11). The company's response clarifies that the calibration factor was derived from a scenario in which the model reflected the subsequent therapies received by patients enrolled in ADAURA,[36] and the calibrated model was then re-adjusted to reflect current UK pathways. However, the company's response also states that the Excel Solver function cannot be made available in the current model. As such, the EAG is unable to fully verify how the calibration method was implemented, or how well the calibrated model fits

the observed OS in ADAURA. Changing any of the parametric survival models for TP1-8 may mean that re-calibration is required, but this cannot be done or determined in the version of the executable model provided by the company.

- The calibration exercise involved applying a single common HR to three sets of survival models used to inform TP4, TP6 and TP8. This HR is treated as a fixed value which is not sampled in the PSA. The company's clarification response[42] (question C11) states that if separate calibration factors were used for TP4, TP6 and TP8, there would be *"endless combinations"* of potential parameter sets which minimise the mean squared error (MSE) between observed and model-predicted OS. The company's response also states that health economic and clinical experts preferred the use of a single common calibration factor rather than separate calibration factors applied to each transition probability. The EAG agrees that there might be multiple combinations of potentially plausible transition-specific calibration factors which can provide a good fit to the ADAURA OS data. The EAG also notes that the fact that the model can minimise the MSE for OS via a single common calibration factor provides no reassurance that the derived calibration factor is correct, and that excluding this variable from the PSA underestimates uncertainty. However, the EAG also acknowledges that applying transition-specific HRs within the calibration, using more complex meta-heuristics, or deriving and sampling from correlated sets of transition-specific calibration factors in the PSA would increase computational expense in evaluating the model.
- The application of the calibration factor within the economic model does not appear to be fully consistent across all transitions. For example, the calibration factor is applied to patients who are re-treated with osimertinib in DM1 (part of TP6), but is not applied to patients receiving PDC in DM1 (another part of TP6). This issue is likely to be minor.

Overall, the EAG agrees that there are likely to be prognostic differences between patients under active monitoring who experience distant relapse, and patients with newly diagnosed metastatic NSCLC in FLAURA.[39] As such, it is unsurprising that without additional adjustment, the model-predicted OS does not provide a good representation of observed OS in ADAURA.[36] The EAG believes that the company's calibration approach for adjusting OS is pragmatic, but that it should be viewed with caution for the reasons discussed above.

(8) Issues relating to utility values

The company's current model includes a disutility for decreased ejection fraction which was not included in the original model used to inform TA761.[20] With the exception of this amendment, the utility values applied in the current model remain unchanged from the company's original model used in TA761.

In TA761,[20] the ERG raised three concerns regarding the utility values included in the company's model:

(i) The utility value applied in the DF and LRR health states was higher than that of the age- and sex-matched general population and was therefore implausible.
(ii) The utility value applied in the DM1 state appeared to be implausibly high, as this was very close to general population utility.
(iii) The model did not include HRQoL decrements for potential late effects of adjuvant treatment or AEs associated with downstream treatments.

The previous ERG report for TA761[20] highlighted that the high utility value applied in the DM1 state (utility = 0.794) did not necessarily favour the adjuvant osimertinib group, as fewer patients are predicted to experience distant metastases following adjuvant treatment compared with those receiving active monitoring alone. The ERG also highlighted that although late effects such as chronic fatigue, immunosuppression, recurrent infections and cardiac and pulmonary toxicity due to adjuvant osimertinib may result in lower HRQoL, there are limited data with which to quantify these impacts. The ERG also highlighted that the company's model did not include detrimental effects associated with AEs resulting from downstream treatments, which would disadvantage adjuvant osimertinib. The TA761 guidance document concluded that the utility values applied in the company's model were acceptable for decision-making. The issues identified above remain in the company's current model. The ERG's full critique of these issues can be found in Section 5.3.4 (critical appraisal point 10) of the earlier ERG report; for brevity, this has not been reproduced here.

The EAG notes two other minor outstanding issues relating to the utility values applied in the current model. Firstly, the model includes age-adjustment of utility values using Ara and Brazier.[73] Hernández Alava *et al.*[74] represents a more recent source of UK general population EQ-5D-3L values. Secondly, the utility value applied in the DF and LRR states is slightly higher than the age- and sex-matched general population EQ-5D-3L estimate, regardless of which source of general population EQ-5D is used. As such, the company's model implies that patients who have early-stage NSCLC have improved HRQoL compared to the general population (see Table 52). The EAG does not consider this to be a reasonable assumption. The ERG in TA761 rectified this issue by capping the DF/LRR utility value at the general population EQ-5D-3L value. However, this cap has been removed from the current version of the company's model.

Table 52: DF/LRR utility value from ADAURA versus age- and sex-matched general population utility

Utility value source	Value
DF/LRR estimated using ADAURA[2] applied in company's model	0.825
General population EQ-5D-3L for age- and sex-matched population using Ara and Brazier[73]	0.809
General population EQ-5D-3L for age- and sex-matched population using Hernández Alava *et al.*[74]	0.821

DF - disease-free; LR - loco-regional recurrence; EQ-5D-3L - Euroqol 5-Dimensions (3-level)

(9) Exclusion of EGFR testing costs from the company's model

The final model used to inform TA761[20] included the costs associated with EGFR mutation testing, and took into account the number of patients that needed to be tested to identify one patient with an EGFR mutation. The final NICE scope for the current appraisal[33] states: *"The economic modelling should include the costs associated with diagnostic testing for EGFR in people with resectable, early-stage NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test."* The company's model for the current appraisal excludes all costs associated with EGFR mutation testing. A sensitivity analysis around EGFR testing costs is not presented in the CS.[2]

During the clarification process, the EAG asked the company to include the costs of EGFR testing in an updated version of the economic model (see clarification response,[42] question C38). The company provided an updated model but did not include these costs. In their clarification response, the company stated: *"Multi-target NGS [next-generation sequencing] panel testing, which includes EGFR, is included in the NHS national genomic test directory and is part of routine care for all early-stage NSCLC patients. As such, the testing cost is common to both arms of the trial and has not been included."*

The EAG sought further information from their clinical advisors regarding whether it is appropriate to include EGFR testing costs in the economic model. The clinical advisors commented that prior to the availability of adjuvant osimertinib, EGFR testing was not conducted for patients without metastatic NSCLC. One clinical advisor highlighted that some centres may test EGFR only rather than using multi-target NGS. They also commented that the costs of EGFR testing are not solely attributable to osimertinib, because testing is also required for some patients to determine whether they would be eligible for neoadjuvant treatment with nivolumab, and that if adjuvant osimertinib was no longer available, EGFR testing would still be required. Both clinical advisors commented that EGFR re-testing may be required, for example, if the recurrence interval is longer or if the pattern of recurrence is atypical.

Overall, the EAG believes that some of the costs of EGFR testing are attributable to adjuvant osimertinib and that these should be considered, at least in sensitivity analyses.

(10) Inclusion of non-reference case discount rates in company's scenario analysis

The 2022 NICE Methods Manual[92] states that the Appraisal Committee may consider non-reference-case discount rates of 1.5% for costs and health effects if all of the following three criteria are met:

- The technology is for people who would otherwise die or have a very severely impaired life
- It is likely to restore them to full or near-full health
- The benefits are likely to be sustained over a very long period.

The CS[2] includes the results of a non-reference case scenario analysis whereby health outcomes and costs for cured patients are discounted at a rate of 1.5%, and health outcomes and costs for uncured patients are discounted at a rate of 3.5% (see Table 47, Scenario SA8). The proportion of patients who are uncured or cured changes depends on the model cycle, increasing from 0% to 95% over the course of the warm-up period (see Figure 11).

The EAG considers the company's scenario analysis to be problematic for two reasons. Firstly, it is not clinically possible to identify which patients should be considered cured or not cured, at least until the assumed final cure timepoint has been reached. The company's clarification response[42] (question C40) states that they considered this to be a conservative approach. The EAG is unaware of this approach being used in any other NICE appraisal. Secondly, as discussed in critical appraisal point (3), there remains uncertainty around the additional curative potential of adjuvant osimertinib compared with active monitoring. A proportion of patients receiving active monitoring will not experience disease relapse, and it may be the case that if osimertinib delays rather than prevents recurrence, then the proportion of osimertinib-treated patients achieving cure would be similar to that for active monitoring alone. Based on this reasoning, the EAG does not believe that non-reference-case discounting should be considered in this appraisal.

(11) Absence of an economic subgroup analysis by disease stage

The final NICE scope[33] states that *"If the evidence allows the following subgroups will be considered: NSCLC stage (1b versus 2-3a) may be considered."* The CS[2] does not report any economic subgroup analyses. Section B.1.1 of the CS states that *"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."* The CS also states that the subgroups considered in ADAURA,[36] which were based on demographics, cancer staging, EGFR mutation, and adjuvant chemotherapy, were not powered to detect significant effects.

During the clarification round, the EAG asked the company to conduct a subgroup analysis to assess the cost-effectiveness of adjuvant osimertinib versus active monitoring for patients with Stage IB disease (see clarification response,[42] question C13). The company did not undertake the analysis

requested by the EAG. The company's clarification response highlights the clinical need for adjuvant treatment in people with Stage IB NSCLC and refers to the consistent benefit in DFS observed across all subgroups in ADAURA. The response also states that the available data for the Stage IB subgroup ADAURA include only 19 recurrence events in the adjuvant osimertinib group and 44 recurrence events in the placebo group, and that given the limited data, it would be inappropriate to assess the cost-effectiveness of osimertinib in patients with Stage IB NSCLC.

The EAG acknowledges that the available data for the stage IB subgroup in ADAURA[36] are subject to small numbers of events which, in turn, will lead to considerable uncertainty around the estimated ICER. However, the absence of economic subgroup analyses means that heterogeneity cannot be explored.

5.4 Summary of the company's revised model

As part of the company's clarification response,[42] the company provided two updated versions of the economic model. The second updated version of the model includes the following amendments:

- The correction of model errors (see Section 5.3.6, critical appraisal point 1, issues a, b-i (except for the docetaxel cost issues), b-ii, b-iv, d,e, and f).
- Additional functionality to undertake scenario analyses which exclude the calibration factor
- Additional functionality to undertake scenario analyses which use age-adjusted utility values from Hernández Alava *et al*.[74]
- Additional functionality to undertake scenario analyses to cap the utility value in the DF state by the general population EQ-5D-3L utility value estimated using Hernández Alava *et al*.[74]
- Additional functionality to undertake scenario analyses to extend disease management costs for all patients in the DF state to 8 years in the adjuvant osimertinib group and 5 years in the active monitoring group.

The company provided an updated base case analysis which included the correction of errors listed in the first bullet point above; other amendments were presented as scenarios analyses only. The company's updated base case results are shown in Table 53. The deterministic base case ICER for adjuvant osimertinib versus active monitoring was reduced from £18,967 per QALY gained to £15,656 per QALY gained. The updated probabilistic ICER is similar at £16,485 per QALY gained.

Table 53: Company's updated base case results following clarification

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Probabilistic model							
Adjuvant osimertinib	[redacted]†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£16,485**
Active monitoring	[redacted]†	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£15,656**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental
** Undiscounted*
† Generated by the EAG by modifying the company's VBA sub-routine for performing PSA

The EAG notes that most of the errors described in point 1 of the EAG's critical appraisal (Section 5.3.6) have been addressed in the company's updated model, except for the error relating to the cost calculations for docetaxel. As illustrated in Figure 39, the updated model omits the costs of docetaxel in the osimertinib re-treated group. In their response to clarification question C28,[42] the company states that this is not an error and justifies that part of the formulae included in the cost calculations, *(1-(prop_IMPower_followingTKI*(1-dm1_retreatment_perc_chemo)))*, *"serves as a catch-all for all patients who do not receive the ABCP-regimen in DM2 and therefore receive chemotherapy instead*." In addition, the company's response to the EAG's follow-on clarification questions stated that *"By default, the percentage of patients receiving second-line docetaxel after PDC in the osimertinib re-treated sub-model are set to 0%"*. Therefore, the company's model calculations assume that 90% of patients in the osimertinib re-treated sub-model receive only PDC and no patients in the re-treated sub-model receive docetaxel. This is not consistent with the treatment pathway described in CS[2] Table 41, and in Table 23 of this EAG report. The cause of this error is likely to be because the company has chosen to route all patients experiencing distant relapse after 4 years in the adjuvant osimertinib group into the osimertinib re-treatment sub-model, even though 50% of these patients are assumed to receive PDC instead of re-treatment with osimertinib in DM1. As described in Table 54, 40% of patients should receive PDC and 50% should receive docetaxel in DM2. This error is corrected in the EAG's exploratory analyses.

Table 54: Expected percentage of patients receiving treatment in DM2 after 48 months in osimertinib arm

Excepted % of patients receiving specific treatments in DM2	Company's original and updated models	EAG's correction
PDC (80% of 50% of patients re-treated with osimertinib in DM1)	90%	40%
ABCP (20% of 50% of patients re-treated with osimertinib in DM1)	10%	10%
Docetaxel (100% of 50% of patients treated with PDC in DM1)	0%	50%

EAG External Assessment Group; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; PDC - pemetrexed plus cisplatin; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel

5.5 Exploratory analyses undertaken by the EAG

5.5.1 Exploratory analysis methods

The EAG undertook exploratory analyses (EAs) using the second updated model provided in the company's clarification response.[42] All analyses were undertaken using the deterministic version of the model. The results of the EAG's preferred analyses are presented using both the probabilistic and deterministic versions of the model. Given the uncertainty surrounding the probability and timing of cure following adjuvant osimertinib, the EAG's preferred analyses are presented across two scenarios: (i) an optimistic scenario which retains the company's base case assumptions of cure, and (ii) a pessimistic scenario in which the warm-up period is removed from both groups, and a final cure timepoint is applied at 8 years in adjuvant osimertinib group and at 5 years in active monitoring group.

All analyses were undertaken by one modeller and checked by a second modeller. All analyses presented in this section reflect the relevant PAS discount for adjuvant osimertinib. The results of the analyses including price discounts for other treatments (PDC, afatinib, atezolizumab and bevacizumab) are provided in a separate confidential appendix to this report.

EAG's preferred analysis

EA1: Correction of errors

The following corrections were applied to the company's model within a single combined analysis:

- *EA1a:* General population mortality was modelled using a weighted survival model. The EAG applied a different approach to that used in the company's second revised model, as the company's revised approach was not mathematically correct (it divided annual probabilities by 12 to obtain monthly probabilities).
- *EA1b:* The model was amended to use life tables for England rather than those for the UK.
- *EA1c:* TP8 for patients who enter the re-treatment sub-model in the osimertinib treatment group was estimated based on the weighted survival of 50% from TP8(a) and 50% from TP8(b), thereby reflecting the treatment pathway illustrated in Figure 39.
- *EA1d:* Administration/monitoring and acquisition costs for docetaxel were included for patients who progress after being treated with PDC in DM1 in the re-treatment sub-model, thereby reflecting the treatment pathway illustrated in Figure 39.
- *EA1e:* The per-cycle treatment duration of carboplatin and paclitaxel was amended from 2.8 to 2.1 model cycles to reflect the dosing approach in IMPower150.[40]

All subsequent EAG exploratory analyses include the error corrections included in EA1.

EA2: Application of general population EQ-5D-3L values from Hernández Alava *et al*.

This analysis applies the general population EQ-5D-3L estimate of 0.821 from Hernández Alava *et al.*[74] in the DF and LRR states of the model. In addition, utility values were adjusted for age using this same source.

EA3: Inclusion of DF disease management costs for all patients until the final cure timepoint in both groups

This analysis includes disease management costs for all patients in the DF state until the final cure timepoint in each treatment group. This was implemented using additional functionality included in the company's updated model.

EA4: Inclusion of wastage for both osimertinib and early TKI treatment

In line with the ERG's preferred analysis in TA761,[20] this analysis includes an assumption of drug wastage for all patients receiving oral TKIs. Wastage costs are applied to: (i) patients who discontinue adjuvant osimertinib before reaching the 3-year maximum treatment duration; (ii) patients who receive osimertinib as first-line treatment for distant metastases and leave the DM1 state, and (iii) patients who receive an early generation TKI as first-line treatment for distant metastases. The analysis assumes that patients will, on average, waste half a pack of osimertinib or early generation TKI.

EA5: Removal of the warm-up period in both groups

This analysis excludes the warm-up period from both treatment groups. Patients are assumed to be cured after 8 years in the adjuvant osimertinib group and after 5 years in the active monitoring group. These assumptions are consistent with the ERG's pessimistic scenario considered in TA761.[20]

EA6: EAG preferred analysis (optimistic scenario)

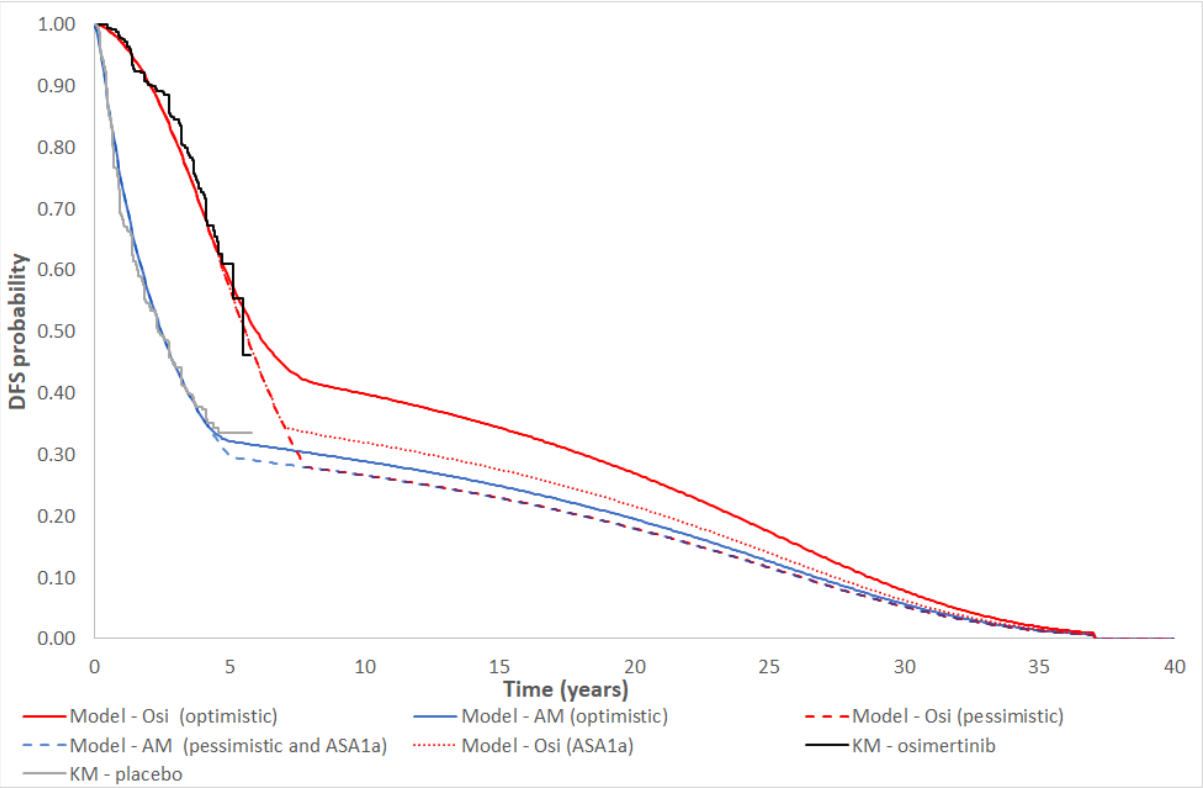
This analysis combines EAs 1-4. Results are presented using both the deterministic and probabilistic versions of the model (EA6a and EA6b, respectively).

EA7: EAG preferred analysis (pessimistic scenario)

This analysis combines EAs 1-5. Results are presented using both the deterministic and probabilistic versions of the model (EA7a and EA7b, respectively).

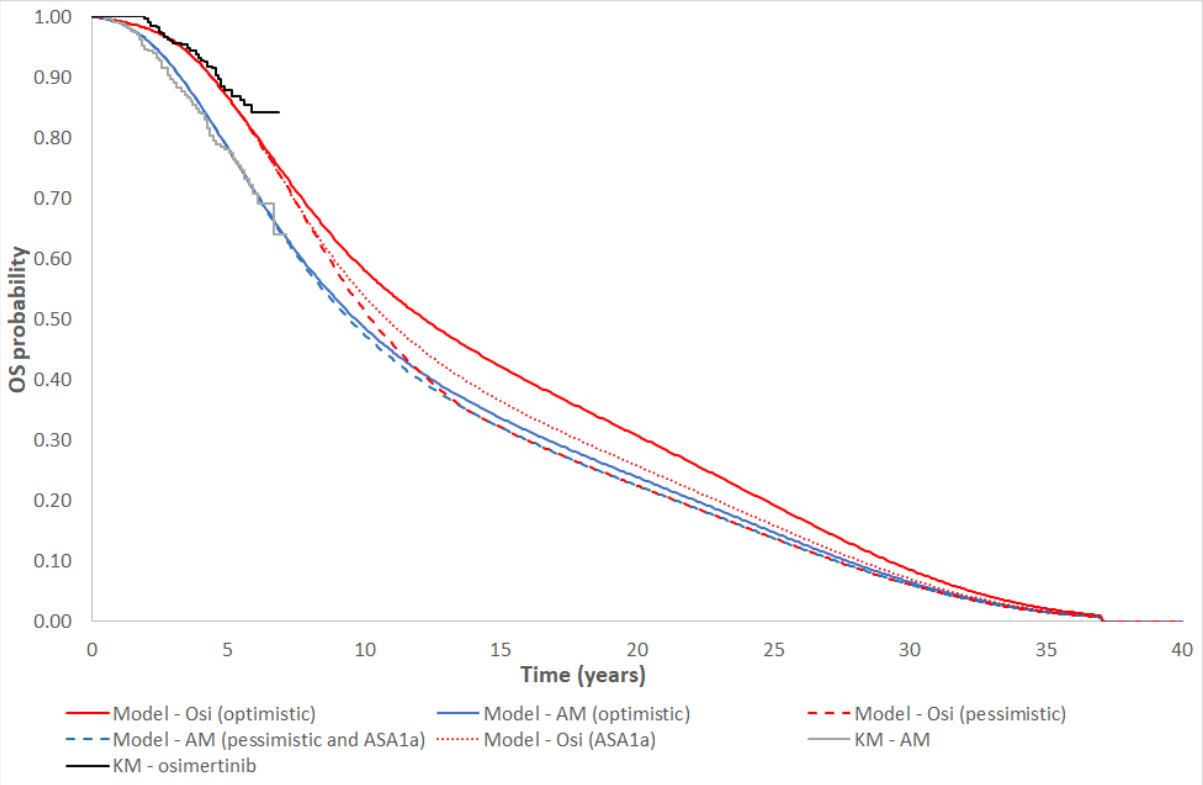
A plot of model-predicted DFS for the EAG's preferred optimistic and pessimistic scenarios (EAs 6 and 7) is presented in Figure 46. The equivalent plot of model-predicted OS is presented in Figure 47. In each of these plots, the solid red and blue lines reflect the optimistic scenario, whereas the dashed red and blue lines reflect the pessimistic scenario.

Figure 46: Model-predicted DFS for the EAG's preferred optimistic and pessimistic analyses



Osi - osimertinib; AM - active monitoring; KM - Kaplan-Meier

Figure 47: Model-predicted OS for the EAG's preferred optimistic and pessimistic analyses



Osi - osimertinib; AM - active monitoring; KM - Kaplan-Meier

Additional sensitivity analyses

The following additional sensitivity analyses (ASAs) were conducted using the deterministic versions of the EAG's optimistic and pessimistic preferred analyses (EA6a and EA7a).

ASA1a: A "middle-ground" scenario. This analysis is based on the EAG's preferred pessimistic scenario (EA7a). The cure timepoint in the adjuvant osimertinib group was moved forward to 7 years. The warm-up period was excluded for both treatment groups. The impact of this assumption on model-predicted DFS and OS for adjuvant osimertinib is shown by the dotted red lines in Figure 46 and Figure 47.

ASA1b: Cure proportion for adjuvant osimertinib group equal to 1-TTD function + 5 years. This analysis is based on the EAG's preferred pessimistic scenario (EA7a). The cure timepoint in the adjuvant osimertinib group was set equal to one minus the TTD function plus 5 years. This scenario is intended to reflect an assumption whereby the cure timepoint for osimertinib is dependent on when the patient discontinues adjuvant therapy.

ASA2a-h: Alternative parametric survival models. The analysis was re-run using alternative survival models for TP1 and TP2. In the osimertinib group, the Gompertz, Weibull, log-logistic and generalised gamma models were explored for TP1, and the Gompertz and Weibull models were explored for TP2. In the active monitoring group, the Gompertz model was explored for TP1 whereas the Weibull model for TP2. Each alternative survival model was evaluated separately.

ASA3a-d: Alternative assumptions regarding the use of osimertinib as first-line treatment (as re-treatment and in patients relapsing under active monitoring). These analyses explore the impact of alternative assumptions around the proportion of patients who receive osimeritnib as first-line treatment for metastatic disease. ASAs 3a-c explore osimertinib re-treatment percentages of 60%, 70% and 80%. ASA3d explores a scenario in which 100% of patients with distant metastases are treated with first-line osimertinib in both groups of the model (note – the re-treatment timepoint was not amended in this scenario).

ASA4: Alternative proportions of patients receiving whole brain radiotherapy and stereotactic radiotherapy. Based on advice from the ERG's clinical advisors in TA761[20] and clinical advisors for the current appraisal, this analysis explores the impact of assuming that 34% of patients with CNS metastases undergo whole brain radiotherapy and 66% undergo stereotactic radiotherapy.

ASA5: Earlier re-treatment timepoint of 36 months. The EAG's clinical advisors suggested that patients who discontinue osimertinib during the earlier months of their adjuvant treatment might be suitable for re-treatment in the metastatic setting earlier than 4 after starting adjuvant therapy. This analysis explores the impact of reducing the osimertinib re-treatment timepoint from 4 years to 3 years.

ASA6: Relative treatment effect for osimertinib in DM1 capped at 5 years. For consistency with the Final Appraisal Determiniation (FAD) for TA654,[21] this analysis assumes that the relative treatment effect for osimertinib in DM1 is applied for 5 years. After this point, the hazard for the comparator group is applied.

ASA7:Inclusion of EGFR testing costs. This analysis includes the costs of EGFR tests for all patients in the adjuvant osimertinib group, and for all patients who experience metastatic relapse and receive a TKI in DM1 in the active monitoring group. The analysis assumes a test cost of £219.39, based on an uplifted cost of the therascreen EGFR test used in NICE Diagnostics Guidance (DG) No. 9.[98] The analysis assumes that 10 patients need to be tested in order to identify one patient with an EGFR mutation. These assumptions are consistent with those used in TA761.[20]

ASA8: Use of utility values from LuCaBIS. Within this analysis, alternative utility values reported by Andreas *et al.*[19] were included in the model (health state utility values: DF=0.72; LRR=0.62; DM1 and DM2=0.59). This analysis is equivalent to a scenario analysis presented in the CS^2 (see Table 47, Analysis SA9).

5.5.2 Exploratory analysis results

Results of EAG's preferred analysis

The results of the EAG's preferred analyses are shown in Table 55. The correction of the remaining model errors slightly reduces the ICER for adjuvant osimertinib versus active monitoring from £15,656 to £15,259 per QALY gained (EA1). Including a cap on the utility value for the DF/LRR states and age-adjusting utility values using Hernández Alava *et al.*[74] and including drug wastage costs have only minor impacts on the ICER (EA2 and EA4). Including disease management costs up to the final cure timepoint also has a fairly small impact on the error-corrected ICER, resulting in an increase from £15,259 to £17,198 per QALY gained (EA3). Removing the warm-up period and applying the final cure timepoints at 8 years for adjuvant osimertinib and at 5 years for active monitoring increases the ICER substantially to £51,452 per QALY gained (EA5). The EAG's preferred analysis results in a probabilistic ICER of £16,991 per QALY gained for the optimistic scenario (EA6b) and £45,677 per QALY gained for the pessimistic scenario (EA7b). The deterministic ICER for the EAG's preferred optimistic analysis is similar to the probabilistic estimate, at £17,156 per QALY gained (EA6a). The deterministic ICER for the EAG's preferred pessimistic analysis is noticeably higher than the probabilistic estimate, at £51,952 per QALY gained (EA7a). The EAG notes that this discrepancy appears to be driven by the probabilistic sampling from the log-logistic distribution for TP2 in the osimertinib group.

Table 55: EAG's preferred model results including PAS discount for adjuvant osimertinib

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's second revised base case							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£15,656**
Active monitoring	[redacted]	[redacted]	[redacted]				
EA1: Correction of remaining model errors							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,259
Active monitoring	[redacted]	[redacted]	[redacted]				
EA2: Using Hernández Alava *et al.* to cap DFS/LRR utility values and for age-adjustment							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,937
Active monitoring	[redacted]	[redacted]	[redacted]				
EA3: All patients incur DFS costs until the final cure time point							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,198
Active monitoring	[redacted]	[redacted]	[redacted]				
EA4: Inclusion of wastage costs for osimertinib and early TKIs							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,586
Active monitoring	[redacted]	[redacted]	[redacted]				
EA5: No warm-up period in both groups, patients cure only at 8 years in osimertinib arm and at 5 years in active monitoring arm							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,452
Active monitoring	[redacted]	[redacted]	[redacted]				
EA6a: EAG-preferred optimistic analysis (EA1-4 combined), deterministic							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£17,156**
Active monitoring	[redacted]	[redacted]	[redacted]				
EA7a: EAG-preferred pessimistic analysis (EA1-5 combined), deterministic							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£51,952**
Active monitoring	[redacted]	[redacted]	[redacted]				
EA6b: EAG-preferred optimistic analysis (EA1-4 combined), probabilistic							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£16,991**
Active monitoring							
EA7b: EAG-preferred pessimistic analysis (EA1-5 combined), probabilistic							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,677**
Active monitoring							

PAS - Patient Access Scheme; EAG - External Assessment Group; EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DF - disease-free; LRR - loco-regional recurrence; TKI - tyrosine kinase inhibitor

** Undiscounted*

Results of the EAG's additional sensitivity analysis

The results of the EAG's additional sensitivity analyses are presented in Table 56.

Under the EAG's preferred optimistic scenario, the ICER remains below £30,000 per QALY gained across all scenarios. The ICER is estimated to be markedly higher than the EAG's preferred analysis in the following scenarios:

- When the Gompertz model is used for TP1 or TP2 osimertinib (ASA2a and ASA2f), and;
- When all eligible patients in both treatment groups are assumed to receive osimertinib as first-line therapy in DM1 (ASA3d).

Under the EAG's preferred pessimistic scenario, the ICER is consistently higher than £30,000 per QALY gained across almost all scenarios. The lowest ICERs arise from the following scenarios:

- The "middle-ground" scenario, which applies the cure timepoint for the adjuvant osimertinib group at 7 years (ASA1a), and;
- When the Gompertz model is used for TP1 osimertinib (ASA2a).

All other sensitivity analyses suggest ICERs which exceed £37,000 per QALY gained.

Table 56: EAG's additional sensitivity analysis results, including PAS for adjuvant osimertinib, deterministic

Additional sensitivity analysis	Optimistic scenario – cure at 5 years for active monitoring and 8 years for adjuvant osimertinib, includes warm-up period				Pessimistic scenario – cure at 5 years for active monitoring and 8 years for adjuvant osimertinib, excludes warm-up period			
	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EAG preferred analysis (EA6a/EA7a)	[redacted]	[redacted]	[redacted]	**£17,156**	[redacted]	[redacted]	[redacted]	**£51,952**
ASA1a: Middle ground scenario, EA7a + cure at 7 years for osimertinib and 5 years for active monitoring, no warm-up	Not applicable.				[redacted]	[redacted]	[redacted]	£27,611
ASA1b: Cure proportion of osimertinib group equal to 1-TTD function + 5 years	Not applicable.				[redacted]	[redacted]	[redacted]	£37,387
ASA2a: TP1 osimertinib: Gompertz model	[redacted]	[redacted]	[redacted]	£28,070	[redacted]	[redacted]	[redacted]	£34,077
ASA2b: TP1 osimertinib: Weibull model	[redacted]	[redacted]	[redacted]	£20,365	[redacted]	[redacted]	[redacted]	£46,897
ASA2c: TP1 osimertinib: Log-logistic model	[redacted]	[redacted]	[redacted]	£18,790	[redacted]	[redacted]	[redacted]	£49,094
ASA2d: TP1 osimertinib: Generalised gamma model	[redacted]	[redacted]	[redacted]	£18,790	[redacted]	[redacted]	[redacted]	£49,094
ASA2e: TP1 AM: Gompertz model	[redacted]	[redacted]	[redacted]	£19,479	[redacted]	[redacted]	[redacted]	£50,970
ASA2f: TP2 osimertinib: Gompertz model	[redacted]	[redacted]	[redacted]	£27,963	[redacted]	[redacted]	[redacted]	£63,074
ASA2g: TP2 osimertinib: Weibull model	[redacted]	[redacted]	[redacted]	£21,054	[redacted]	[redacted]	[redacted]	£54,582
ASA2h: TP2 AM: Weibull model	[redacted]	[redacted]	[redacted]	£17,143	[redacted]	[redacted]	[redacted]	£52,999
ASA3a: 60% re-treated group in osi group	[redacted]	[redacted]	[redacted]	£19,369	[redacted]	[redacted]	[redacted]	£54,978
ASA3b: 70% re-treated group in osi group	[redacted]	[redacted]	[redacted]	£21,716	[redacted]	[redacted]	[redacted]	£58,224
ASA3c: 80% re-treated group in osi group	[redacted]	[redacted]	[redacted]	£24,184	[redacted]	[redacted]	[redacted]	£61,636
ASA3d: 100% of all re-treated patients in osi group and 100% of patients with distant relapse in AM group treated with osi	[redacted]	[redacted]	[redacted]	£26,004	[redacted]	[redacted]	[redacted]	£66,961
ASA4: 34% whole brain RT, 66% stereotactic RT	[redacted]	[redacted]	[redacted]	£17,199	[redacted]	[redacted]	[redacted]	£52,458
ASA5: Re-treatment timepoint = 3 years	[redacted]	[redacted]	[redacted]	£19,491	[redacted]	[redacted]	[redacted]	£53,836
ASA6: Treatment effect for osi in DM1 capped at 5 years	[redacted]	[redacted]	[redacted]	£18,707	[redacted]	[redacted]	[redacted]	£53,378
ASA7: EGFR testing costs included	[redacted]	[redacted]	[redacted]	£18,039	[redacted]	[redacted]	[redacted]	£53,743
ASA8: Utility values from LuCaBIS	[redacted]	[redacted]	[redacted]	£17,269	[redacted]	[redacted]	[redacted]	£47,442

EA - exploratory analysis; ASA - additional sensitivity analysis; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; TP - transition probability; RT - radiotherapy; DM1 - first-line treatment for distant metastasis; EGFR - epidermal growth factor receptor

** Undiscounted*

5.6 Discussion

The CS[2] presents an SLR of existing cost-effectiveness analyses of treatments for patients with stage IB–IIIA EGFRm NSCLC following complete tumour resection, and describes the methods and results of the company's model-based health economic analysis of adjuvant osimertinib within this population.

The company's SLR identified four model-based economic analyses of adjuvant treatments for patients with stage IB–IIIA EGFRm NSCLC.[54-57] All three of the included economic analyses of adjuvant osimertinib used a state transition modelling approach, based on ADAURA[36] and external data.[39] The company's SLR did not include the model used to inform TA761.[20] However, the paper reported by Verhoek *et al.*[57] describes a very similar model structure to that used in TA761. The company's model for the current appraisal also applies a similar structure.

The company's submitted model assesses the cost-effectiveness of adjuvant osimertinib versus active monitoring in adults with fully resected, stage IB-IIIA EGFRm-positive NSCLC over a lifetime horizon from the perspective of the NHS and PSS. The population included in the model is consistent with the full marketing authorisation for the adjuvant indication for osimertinib.[32] No subgroup analyses are reported. A comparison against adjuvant chemotherapy was not included. The company's model uses a semi-Markov state transition approach which includes five health states: (i) disease-free; (ii) loco-regional recurrence; (iii) first-line treatment for metastatic disease; (iv) second-line treatment for metastatic disease and (v) dead. Clinical outcomes for patients without relapse are drawn from the most recent DCOs of DFS and OS from ARAURA;[36] outcomes for patients following relapse were informed by external data.[39-41, 71] A calibration approach was applied to some post-relapse transition probabilities to align modelled OS with observed OS in ADAURA. The model includes structural assumptions of cure at 5 years for active monitoring and at 8 years for adjuvant osimertinib, including a warm-up period whereby the reduction in the predicted risk of relapse increases approximately linearly from 0% to 95% in each cycle until the final cure timepoint. Health state utility values were estimated using data from ADAURA, FLAURA and the literature. Resource costs were based on ADAURA, previous NICE appraisals, standard costing sources, literature and clinical assumptions. The model assumes that 50% of patients who receive adjuvant osimertinib and subsequently experience distant relapse after 4 years will be re-treated with osimertinib. Eighty three percent of patients who receive active monitoring and subsequently experience metastatic relapse are also assumed to receive osimertinib as first-line therapy.

The probabilistic version of the company's original model suggests that the ICER for adjuvant osimertinib versus active monitoring is £18,378 per QALY gained. The deterministic ICER is similar. Based on the characteristics of the population and the expected discounted QALY gains in the active monitoring group, severity-related QALY weighting is not applicable. Following the clarification round, the company submitted two revised versions of the economic model which include the correction

of minor errors as well as additional functionality; the company's second updated model suggests a lower probabilistic ICER of £16,485 per QALY gained. This updated model includes some minor errors.

The EAG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The EAG's main concerns regarding the company's economic model are summarised below:

- Despite the availability of additional data from ADAURA,[36] there remains uncertainty around the long-term DFS and OS benefits of adjuvant osimertinib, including uncertainty around the timepoint at which cure is expected for osimertinib-treated patients and the proportion of patients who will be cured. The company has indicated that no further data on recurrence are being collected in ADAURA.
- The company's model predicts a sustained gap in DFS and OS between the adjuvant osimertinib and active monitoring treatment groups. This gap is largely driven by the company's cure assumptions. These assumptions are a key driver of the ICER.
- The EAG's analyses of time-varying hazards in ADAURA indicate that the DFS hazard for the placebo group becomes very low within the observed period of the trial, which provides some support for a cure assumption for active monitoring prior to this timepoint. However, the DFS hazard in the adjuvant osimertinib group increases over the observed period of ADAURA. This does not provide supportive evidence for a cure assumption within the observed period of the trial. The company's cure warm-up assumptions create a turning point in the modelled DFS hazard for the osimertinib group which deviates from what has been observed in the trial.
- The EAG's additional MCM survival analysis provides some support for the company's cure assumptions in the active monitoring group, as broadly consistent cure fractions could be estimated within this group using a range of alternative MCMs. However, the EAG was able to estimate cure fractions for only two MCMs in the adjuvant osimertinib group. This does not mean that osimertinib is not curative, but it does suggest that the available data from ADAURA are not sufficiently mature to provide evidence to support this assumption.
- One of the EAG's clinical advisors considered the company's model predictions of DFS and OS to be clinically plausible but uncertain, whereas the other clinical advisor was unsure whether the gap in DFS and OS between the treatment groups would be maintained in the longer-term.
- There is remaining uncertainty around the proportion of patients who would receive re-treatment with adjuvant osimertinib following metastatic relapse. This aspect of the company's model has not been updated since TA761,[20] and no new data have been provided.

The EAG also identified other additional issues relating to model errors, the utility values applied in the model, and some of the costing assumptions. These issues are less important than the modelled cure assumptions.

The EAG undertook exploratory analyses using the company's second revised model provided following the clarification process. The EAG's preferred model includes: (1) the correction of additional minor programming errors; (2) the use of Hernández Alava *et al.*[74] to age-adjust utility values and to cap the utility value for the DF and LRR states; (3) the inclusion of disease management costs for all patients without relapse until the final cure timepoint in both treatment groups, and (4) the inclusion of drug wastage costs for all oral TKIs, including osimertinib. Owing to uncertainty around the company's assumptions of cure, and the limitations of the available data from ADAURA,[36] the EAG's exploratory analyses include an optimistic scenario which retains the company's cure assumptions, and a pessimistic scenario which removes the warm-up period from both treatment groups. The final cure timepoints remain the same across both scenarios. Under the EAG's preferred optimistic scenario, the EAG's preferred probabilistic ICER is £16,991 per QALY gained, whereas under the EAG's preferred pessimistic scenario, the ICER is £45,677 per QALY gained. The deterministic ICER for the optimistic scenario is similar to the probabilistic estimate; however, the deterministic ICER for the pessimistic scenario is noticeably higher, at £51,952 per QALY gained. The EAG's additional sensitivity analyses indicate that the ICERs are most sensitive to the cure assumptions and the proportion of patients assumed to receive osimertinib as treatment for metastatic disease in both treatment groups (including as re-treatment). The choice of parametric survival model for TP1 and TP2 also have some influence on the ICER.

6. OVERALL CONCLUSIONS

6.1 Clinical effectiveness conclusions

The updated analyses of ADAURA, which are based on DCOs of April 2022 for DFS and January 2023 for OS, suggest treatment benefits in favour of adjuvant osimertinib compared with placebo. In the overall population, median DFS was 65.9 months and 28.1 months in the adjuvant osimertinib and placebo groups, respectively. The HR for DFS for osimertinib versus placebo was 0.27 (95% CI 0.21 to 0.34, *p*=NR). In the overall population, median OS was not reached in either treatment group. The HR for OS for osimertinib versus placebo was 0.49 (95% CI 0.34 to 0.70, *p*<0.0001). DFS and OS benefits in favour of adjuvant osimertinib were demonstrated regardless of prior adjuvant chemotherapy use. A benefit in CNS DFS was reported for osimertinib in the overall population (HR 0.36, 95% CI 0.23 to 0.57, *p*=NR). [redacted] Efficacy results for the stage II-IIIA subgroup of ADAURA were generally consistent with those for the overall population. In the overall population, 11% of patients had treatment-related Grade≥3 AEs in the osimertinib group compared with 2% in the placebo group. The EAG's clinical advisors considered that the ADAURA trial is generalisable to the population of patients who would be eligible to receive adjuvant osimertinib in the NHS in England. Alongside ADAURA, the CS also reports data on patient characteristics, treatment duration and OS from SACT; however, these are limited by the short duration for which osimertinib has been available, with 80% of patients still receiving osimertinib treatment at the time of the analysis. No data on re-treatment rates were available from SACT or from any other source.

Despite the availability of updated DCOs, there remains uncertainty around the long-term benefits for osimertinib, in particular, its curative potential. The Kaplan-Meier curve for DFS in the placebo group suggests that the function begins to plateau at around 48 months, whereas the Kaplan-Meier curve for osimertinib suggests a continued risk of recurrence beyond this timepoint. In addition, the maturity of the OS data remains low at 18%. It remains uncertain whether the benefit in DFS and OS seen in ADAURA would be maintained with additional follow-up.

6.2 Cost-effectiveness conclusions

The company's economic model assesses the cost-effectiveness of adjuvant osimertinib versus active monitoring for the treatment adults with fully resected, stage IB-IIIA EGFRm-positive NSCLC. The severity-related decision modifier for all analyses presented by the company and the EAG is 1.0. The second updated version of the company's model, which includes the correction of most of the errors identified by the EAG, suggests that the probabilistic base case ICER for adjuvant osimertinib versus active monitoring is £16,485 per QALY gained. This analysis includes cure timepoints of 5 years for active monitoring and 8 years for adjuvant osimertinib, including a warm-up period for the cure assumption in both groups starting after 4 years.

Owing to uncertainty around the company's cure assumptions, the EAG's exploratory analyses are presented for (a) a preferred optimistic scenario which retains the company's cure assumptions, and (b) a preferred pessimistic scenario which retains the final cure timepoints but removes the warm-up period from both groups. The EAG's exploratory analyses also include: (i) the correction of remaining errors; (ii) age-adjusted utility values based on Hernández Alava *et al.*; (iii) the inclusion of disease management costs for patients who remain disease-free until the final cure timepoint in each group, and (iv) the inclusion of drug wastage costs for all TKIs. The EAG's preferred optimistic scenario suggests that the probabilistic ICER for adjuvant osimertinib versus active monitoring is £16,991 per QALY gained. The deterministic ICER is similar, at £17,156 per QALY gained. The EAG's preferred pessimistic scenario suggests that the probabilistic ICER for adjuvant osimertinib versus active monitoring is £45,677 per QALY gained. The deterministic ICER is higher, at £51,952 per QALY gained. The EAG's additional sensitivity analyses indicate that the ICER is sensitive to the cure timepoint in the osimertinib group, the choice of parametric survival model used to estimate the risk of relapse, and the proportion of patients who receive osimertinib as first-line treatment for distant metastases (either as re-treatment in the adjuvant osimertinib group, or as treatment for patients with metastatic relapse in patients receiving active monitoring).

Additional data collection would be required to resolve the remaining uncertainties around long-term effectiveness, cure rates and the extent of use of osimertinib in the metastatic setting. [redacted] The EAG understands that ADAURA has been unblinded and no further data on disease recurrence are being collected.

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Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (review of TA761) [ID5120]

Additional figures and graphs for pre-meeting

Figure 1: Treatment pathway for osimertinib arm

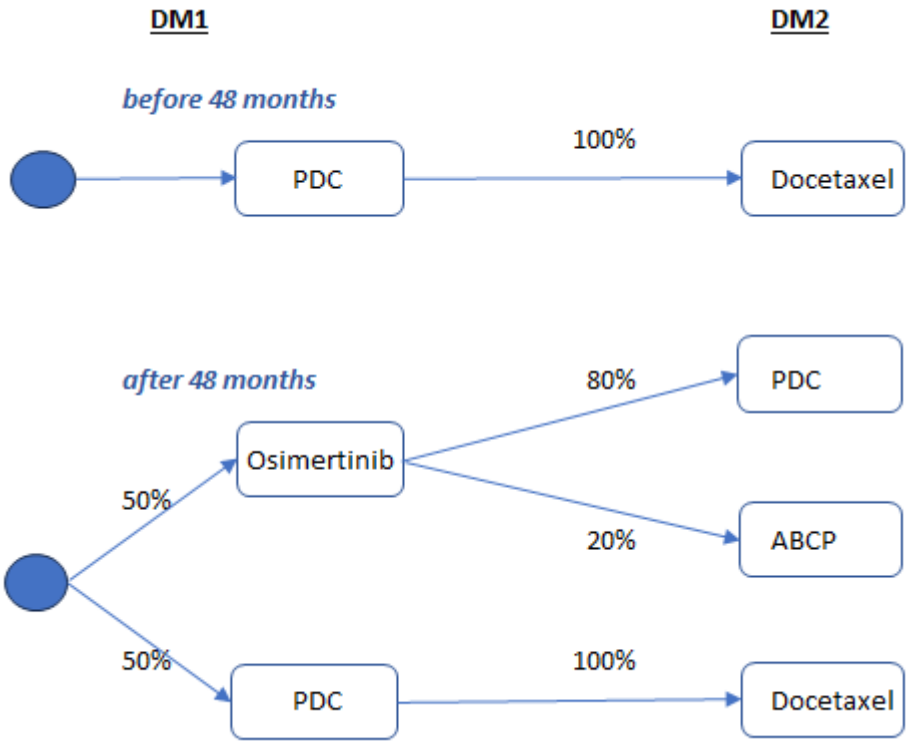

Figure 2: Treatment pathway for active monitoring arm

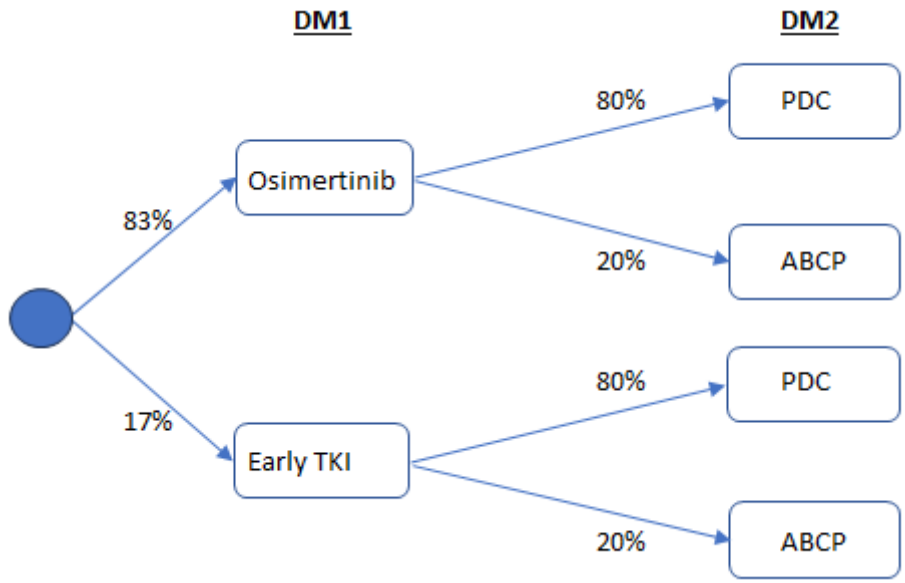

Figure 3: Model-predicted DFS for the EAG's preferred optimistic, pessimistic, ASA1a and ASA1b scenarios

Figure 4: Model-predicted OS for the EAG's preferred optimistic, pessimistic, ASA1a and ASA1b scenarios

Single Technology Appraisal

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (Review of TA761) [ID5120]

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 25 March 2024** 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 Context missing from claim around patient characteristics from SACT

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 33. "Summary data from the Systemic Anti-Cancer Therapy (SACT) database provided in CS Appendix R suggest that NHS patients who have received adjuvant osimertinib are slightly less fit than the ADAURA trial population …"	"Summary data from the Systemic Anti-Cancer Therapy (SACT) database provided in CS Appendix R suggest that NHS patients who have received adjuvant osimertinib are slightly less fit than the ADAURA trial population according to performance status, although it should be noted that 27% of scores were missing."	It is unclear how the EAG concluded that patients were slightly less fit. The Company has assumed this is according to performance status, however, believe this should be clarified in the text. It is also notable that 27% of these scores were missing.	The EAG has amended the text for clarity. "Summary data from the Systemic Anti-Cancer Therapy (SACT) database provided in CS Appendix R[37] suggest that NHS patients who have received adjuvant osimertinib are slightly less fit than the ADAURA trial population, with fewer patients with a PS of 0 in SACT. Fewer patients in SACT received prior adjuvant chemotherapy than in ADAURA (proportion with prior chemotherapy: SACT = 27%; ADAURA = 60%)."

Issue 2 Errors and inconsistencies in Table 20

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 65, Table 20 SACT Females, N (%): 33 (23%) Age≥50 years, N (%): 135 (95%) Inconsistent marking of missing data – i.e., indicated for Prior Chemotherapy and Performance Status, but not for other missing inputs	SACT Females, N (%): 110 (77%) Age≥50 years, N (%): 135 (94%) Other inputs with missing data include 1% missing tumour specimen, 1% missing stage of disease[1]	The table should reflect the correct values from the SACT report and have consistent labelling.	The number and proportion of females have been corrected to reflect data in CS Appendix R, Table 68. Data on the proportion of patients aged ≥50 years and with performance status 0 or 1 were obtained from the text in CS Appendix R, *"Most of the cohort were aged 50 years and over 95% (n=135) and 73% (n=104) of patients had a performance status between 0 and 1 at the start of their regimen*." The percentage of patients aged 50 years and over has been corrected in the EAG report (from 95% to 94%).

			Details of missing data on stage of disease and tumour specimen have now been included in Table 20.

Issue 3 Missing special warnings and precautions of use from SmPC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 34. "Stevens-Johnson syndrome (SJS): Case reports of SJS have been reported rarely in association with osimertinib treatment."	"Severe Cutaneous Adverse Reactions (SCARs): Case reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) been reported rarely in association with osimertinib treatment."	The Company recommend that TEN is included in this list for completeness and in accordance with the SmPC.[2]	The EAG agrees. The company's suggested amendment has been included in the text.

Issue 4 Missing details on trial design

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 33. "DFS outcomes reached the pre-specified level of maturity	Pg 33. "DFS outcomes reached the pre-specified level of maturity (approximately 50% in the stage II–IIIA population) at the April 2022 DCO."	It is important to be clear on the definition of maturity in the trial data, as the	The text has been amended on pages 42 and 48, as suggested by the company.

(approximately 50%) at the April 2022 DCO." Pg 48. "Planned maturity for the DFS analysis was 50%."	Pg 48. "Planned maturity for the DFS analysis was 50% in the stage II–IIIA population."	submission population is broader (Stage IB-IIIA).[3]	

Issue 5 Misrepresentation of quote from Verhoek et al.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 70. "The base case analyses presented in the studies of osimertinib used health state utility values sourced from other literature, rather than from ADAURA. The paper by Verhoek et al. comments that the process of mapping SF-36 utility estimates collected in ADAURA to the EQ-5D-3L made the results "unreliable and not suited for the reference case.""	"The base case analyses presented in the studies of osimertinib used health state utility values sourced from other literature, rather than from ADAURA, as there was no direct mapping algorithm available from SF-36 to EQ-5D with the Canadian tariff applied. ~~The paper by Verhoek et al. comments that the process of mapping SF-36 utility estimates collected in ADAURA to the EQ-5D-3L made the results "unreliable and not suited for the reference case~~.""	The quote regarding the mapping of SF-36 utility estimates collected in ADAURA to the EQ-5D-3L being "unreliable and not suited for the reference case" is misleading and taken out of context, given that Verhoek et al. were referring to the fact that they could not map directly from SF-36 to EQ-5D with Canadian weights using existing algorithms, and therefore had to map via SF-12, and this was the cause of the unreliability.[4] This issue does not apply when	The EAG agrees. The EAG has amended the text in the report.

		mapping from SF-36 to EQ-5D directly using Rowen, as was done in the submission.[5]	

Issue 6 Important context of the maturity of the data missing

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On Pg 136: "The EAG notes that whilst it is possible that further follow-up in ADAURA might lead to a turning point in the hazard for the osimertinib group, this trend has not yet been observed in the available data, despite follow-up out to around 6 years."	"The EAG notes that whilst it is possible that further follow-up in ADAURA might lead to a turning point in the hazard for the osimertinib group, this trend has not yet been observed in the available data. Whilst around 6-years of follow-up has been collected, the failure of 5/7 MCM models to generate cure fractions for the adjuvant osimertinib arm suggests that the available data from ADAURA are not sufficiently mature, and this lack of turning point in the observed hazards should be interpreted with caution".	The EAG conducted the MCM despite the Company explaining that that the data was too immature to produce reliable results. Indeed, the results of the EAGs analyses show that the data are too immature for such analysis. Despite this, the EAG make claims on the observed hazard function for adjuvant osimertinib without providing important context on the immaturity of these data.	We believe that Section 5.3.6 of the EAG report clearly explains this issue already. The EAG believes that caution should be advised when considering the results of the company's base case analysis (and the EAG's optimistic scenario analysis) because it suggests a turning point in the hazard of DFS which has not been observed in the available data from ADAURA. The EAG report has not been amended.

Issue 7 Statement made on double-counting cure without justification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 144 “The EAG considers that selecting a parametric survival model which is intended to be compatible with cure and then applying a structural assumption of cure on that model may be accounting for the cure twice;”	Please could the EAG expand on how cure is accounted for twice, as this is not clear and not explained in the report.	The Company is under the understanding that cure has not been accounted for twice in the model.	The EAG believes that cure is potentially being counted twice: (i) through the rejection of parametric survival models which are not consistent with the company’s expectations of functional cure, and (ii) by applying a structural cure assumption in the economic model whereby the predicted hazards from the selected survival models for DFS events are reduced by 95% after the final cure timepoint (or by a lesser percentage during the warm-up period). After this final cure timepoint, the hazard from all of the survival models for TP1 and TP2 is very low.

			This issue is already explained in Section 5.3.6 of the EAG report.

Issue 8 Misrepresentation of approach taken by the Company

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 144 “(iii) the fit of the aggregated DFS and OS from the economic model to the observed DFS and OS should have also been given more weight, following the recommendations by Williams et al.”	Removal of part (iii)	The Company gave arguably the most weight to clinical opinion when selecting the curves. This sentence misrepresents the approach taken by the Company.	The EAG report does not state that clinical opinion was not used to inform the company’s selection of parametric survival models. The point that we are trying to make is that the CS does not describe an iterative parametric survival model selection approach. Alternative survival models for each individual endpoint should be explored iteratively when competing risks are involved, because the survival probabilities are based on a combination of two or more outcomes

			that are interlinked, rather than just one. With competing risks in the model, the best fitting model for each transition does not necessarily fit the aggregated DFS and OS well. This may be the case with OS, whereby the economic model does not fit the aggregate OS data. This type of iterative model selection approach is suggested by Williams et al. in the context of survival modelling in a competing risks scenario. The EAG notes however, that without evidence of this iterative approach having been used in the CS, it is not possible to say whether it would have improved overall model fit to OS.

			The EAG report has been amended to read: “the fit of the aggregated DFS and OS from the economic model to the observed DFS and OS should have also been given more weight, following the recommendations by Williams *et al.*84 (although the EAG notes that is unclear whether this latter suggestion would have fully resolved the poor fit of the model to the aggregate OS data).”

Issue 9 Errors in number of model cycles

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 73, Table 23, Table footnotes: ‡ Five 21-day cycles correspond to 3.8 model cycles § Four 21-day cycles correspond to 3 model cycles Pg 113 Pg 113 ““Subsequently, 80% of these patients undergo PDC (3.8 model cycles) and … relapse after 48 months receive first-line PDC (3.8 model cycles) followed… either PDC (in 80% of cases for 3.8 model cycles) or..”	Pg 73 ‡ Five 21-day cycles correspond to 3.4 model cycles § Four 21-day cycles correspond to 2.8 model cycles Pg 113 ““Subsequently, 80% of these patients undergo PDC (3.4 model cycles) and … relapse after 48 months receive first-line PDC (3.4 model cycles) followed… either PDC (in 80% of cases for 3.4 model cycles) or..”	The incorrect number of model cycles is referenced in the table footnote, and in subsequent sections in the report.	The EAG agrees. The report has been amended as suggested.

Issue 10 Inconsistency reporting of Company errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 116 and Pg 117, Table 45. The text above the table says “The EAG notes that the cost of decreased ejection fraction is erroneously excluded from the company’s cost calculations in the model”, whilst the Table 45 includes it in the Total cost. It also means that the values in Table 45 does not align with the values in Table 40.	Add a footnote to the table: *this includes the correction made by the Company.	There should be consistency throughout Section 5.2.4 in the EAG report with respect to whether they include the Company corrections or not.	The EAG agrees. A footnote has been added below Table 45. The footnote in Table 40 is still correct, and so it does not require amendment.

Issue 11 Unreferenced claim on drug wastage

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pg 156 “EA4: Inclusion of wastage for both osimertinib and early TKI treatment… The analysis assumes that patients will, on average,	Can the EAG add a source for this assumption and/or provide detail of whether it was validated with clinicians.	There is no evidence provided to support this assumption. The EAG should	The EAG does not consider it reasonable to assume that oral therapy can be given without

waste half a pack of osimertinib or early generation TKI.”		clarity the source of new data introduced.	incurring some level of wastage. We assumed that patients who discontinue treatment without completing the full pack will, on average, waste half a pack of treatment (in both treatment groups of the model, and for all oral TKIs). The assumptions employed in the exploratory analysis EA4 are the same as those employed in the ERG exploratory analyses in TA761. The EAG notes that this is a very minor issue which has a minimal impact on the ICER for osimertinib.

References

1. National Disease Registration Service (NDRS). *Osimertinib for Adjuvant Treatment of EGFR Mutation-Positive Non-Small-Cell Lung Cancer – Data Review*.; 2023.

2. European Medicines Agency. *Tagrisso : EPAR - Product Information*.; 2024. https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf

3. Wu YL, Herbst RS, Mann H, Rukazenkov Y, Marotti M, Tsuboi M. ADAURA: Phase III, Double-blind, Randomized Study of Osimertinib Versus Placebo in EGFR Mutation-positive Early-stage NSCLC After Complete Surgical Resection. *Clin Lung Cancer*. 2018;19(4):e533-e536. doi:10.1016/j.cllc.2018.04.004

4. Verhoek A, Cheema P, Melosky B, et al. Evaluation of Cost-Effectiveness of Adjuvant Osimertinib in Patients with Resected EGFR Mutation-Positive Non-small Cell Lung Cancer. *PharmacoEconomics Open*. 2023;7(3):455-467. doi:10.1007/s41669-023-00396-0

5. Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Health Qual Life Outcomes*. 2009;7(1):27. doi:10.1186/1477-7525-7-27