NICE 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 [ID3835]

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 [ID3835]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from AstraZeneca
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. EGFR Positive UK
   b. Royal College of Pathologists
4. **Evidence Review Group report** prepared by School of Health and Related Research (ScHARR)
5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from** AstraZeneca
7. **Technical engagement responses and statements from experts:**
   a. Eric Lim – clinical expert, nominated by AstraZeneca
   b. Gary Doherty – clinical expert, nominated by AstraZeneca
   c. Andrew Robinson – clinical expert, nominated by the Royal College of Pathologists
   d. Jenny Abbott – patient expert, nominated by EGFR Positive UK
   e. Angela Terry – patient expert, nominated by EGFR Positive UK
8. **Technical engagement responses from consultees and commentators:**
   a. Royal College of Pathologists
   b. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

9. **Evidence Review Group critique of company response to technical engagement** prepared by School of Health and Related Research (ScHARR)

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 2021

File name	Version	Contains confidential information	Date
ID3835_Osimertinib_ Document B_V2_[fully redacted]	**V2.0**	**Yes**	**17th March 2021**

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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

- **This appraisal compares osimertinib with placebo (i.e. active monitoring) with or without adjuvant chemotherapy (representing established clinical management) for the adjuvant treatment of stage IB–IIIA EGFRm-positive NSCLC after complete tumour resection**
    - Osimertinib is a third-generation TKI designed to inhibit EGFR-sensitising mutations and inhibit the emergence of EGFR T790M resistance mutations while having minimal impact against wild-type EGFR.
    - Osimertinib is an oral therapy and is currently reimbursed for the first-line treatment of adult patients with locally advanced or metastatic EGFRm-positive NSCLC, or in patients with T790M mutation-positive EGFR after first-line treatment with an EGFR-TKI
- **Osimertinib offers an unprecedented DFS benefit and is considered a highly innovative and pioneering oncology medicine in the adjuvant treatment of completely-resected patients with stage IB–IIIA EGFRm positive NSCLC[1]**
    - Osimertinib is in development for the treatment of patients with completely resected EGFRm-positive stage IB–IIIA NSCLC (ADAURA trial). Therefore, AstraZeneca are seeking reimbursement for osimertinib for [redacted]
    - Due to the innovative nature of the ADAURA indication and unprecedented magnitude of benefit observed in the trial, osimertinib for the adjuvant treatment of patients with EGFRm-positive NSCLC following complete resection has been reviewed as part of Project Orbis[2]
- Project Orbis is an FDA OCE initiative with a focus on high-impact cancer drugs; providing a framework for concurrent submission and review of oncology products among international partners. In 2020, the MHRA participated as part of Project Orbis as an observer and became a full participant as of 1st January 2021, however, each country remains fully independent on their final regulatory decision. [redacted]
- **Despite the curative intent of complete resection in eligible patients, disease recurrence and mortality rates in EGFRm-positive NSCLC remain high**
    - Surgical resection is the mainstay of treatment for early-stage, resectable NSCLC, and is considered potentially curative[3]
    - Despite complete resection of the tumour, rates of disease recurrence are high and survival outcomes are poor, with 5-year recurrence rates of 45–76% and 5-year mortality rates of 38–70% for patients with stage IB–III NSCLC[4]
    - Of all patients with NSCLC (regardless of whether they experience disease recurrence), those with EGFRm NSCLC have a two-times higher risk of brain

metastases vs wild-type EGFR,[5] which leads to high mortality and imposes a heavy symptom, treatment, and quality of life burden[6, 7]

- **In total, 33% of UK patients with completely resected NSCLC receive adjuvant treatment with chemotherapy; however, this provides only minimal survival benefits[4, 8]**
  - Despite being recommended clinical practice, adjuvant chemotherapy confers only a 5.4% and 5.8% absolute benefit for 5-year OS and DFS, respectively, compared with no chemotherapy[4]
  - Due to the small perceived benefit and substantial AE profile, many patients choose not to receive adjuvant chemotherapy, with 95% at stage IB to 50% at stage IIIA placed under routine surveillance without receiving any adjuvant therapy post resection; therefore, in current clinical practice, patients with stage IB–IIIA NSCLC receive complete resection followed by active monitoring with or without adjuvant chemotherapy. As osimertinib is positioned for use in the same setting, the comparator for this submission is active monitoring (placebo with or without chemotherapy)[3, 9]
- **Beyond the addition of adjuvant chemotherapy, there has been little innovation in this treatment setting in 20 years, and there is a clear unmet need for targeted, efficacious and well-tolerated treatment options for patients with EGFRm-positive NSCLC following complete resection[10]**
  - Despite high mortality after resection, chemotherapy remains the only adjuvant option to increase disease-free survival after surgery, of which the incremental benefit is low[3, 4]
  - Previous trials of targeted first-generation EGFR-TKI therapies in the adjuvant setting showed poor disease control (including no long-term DFS or OS benefit) thought to be partly due to poor blood-brain barrier penetration, meaning EGFR mutations remain an underutilised therapeutic target[11-13]
  - Limitations of previous adjuvant EGFR-TKI trials included: not multi-national in design or limited generalisability to the UK completely-resected NSCLC population; open-label design; treatment limited to 2 years; a population not limited to EGFRm-positive patients; and inclusion of patients without negative margins[12, 14-16]
- **The ADAURA trial of third-generation EGFR-TKI osimertinib was recommended for early unblinding by the independent data monitoring committee due to unprecedented DFS benefit, and demonstrated significant improvements in CNS recurrence or death vs placebo[1, 17] (see Section B.2)**
  - ADAURA is a multi-national, double-blind trial which randomised patients with completely-resected (negative margins) EGFRm-positive NSCLC to either 3-year treatment with osimertinib or to placebo[17]

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 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 anticipated full marketing authorisation for this indication and is in line with the scope issued by the National Institute for Health and Care Excellence (NICE) (Table 1). The indication wording for osimertinib proposed by AstraZeneca is as follows: [redacted]

The submission presents data for the following outcomes 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.

Comparator

The decision problem states that *established clinical management without osimertinib (that is, active monitoring)* is a relevant comparator for this appraisal. Surgical removal of the tumour with the aim of complete resection is the mainstay of treatment of resectable NSCLC. Postoperative adjuvant cisplatin-based chemotherapy is recommended after complete resection to reduce the risk of recurrence, and should be offered to all patients with good performance status (PS; World Health Organization [WHO] 0–1) and nodal involvement or large (>4 cm) primary tumours.[3] Many patients do not receive adjuvant chemotherapy, with the proportion who do increasing with disease advancement, and few patients with stage IB receive adjuvant therapy unless deemed high risk; this was validated by a survey of six UK clinicians.[9] After completion of surgery with or without adjuvant chemotherapy, patients remain under active monitoring for disease recurrence, with no further therapies available;[3] after 5 years of follow-up (in the absence of disease recurrence), patients are generally considered cured and discharged from their care.[18] Therefore, there are no active comparators in this appraisal.

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 EGFR mutation-positive NSCLC after complete tumour resection (with or without adjuvant chemotherapy)	As per scope	N/A
Intervention	Osimertinib (as an adjuvant treatment)	As per scope	N/A
Comparator(s)	Established clinical management without osimertinib (that is, active monitoring)	As per scope	N/A
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 for EGFR in people with resectable, early-stage NSCLC who would not	The economic base case is based on the NICE reference case. Confidential commercial arrangements, including a patient access scheme (PAS) is applicable for osimertinib for treating EGFR T790M mutation-positive advanced NSCLC (TA653) and osimertinib for untreated EGFR mutation-positive NSCLC (TA654). [redacted]	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.		
Subgroups to be considered	If the evidence allows, subgroups based on NSCLC stage (Ib versus II-IIIa) may be considered.	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 were based on demographics, cancer staging, EGFR mutation, and adjuvant chemotherapy. 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.	N/A
Special considerations including issues related to equity or equality	-	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 the sensitising and T790M mutant forms of the EGFR-TK
Marketing authorisation/CE mark status	Current EMA marketing authorisation of osimertinib is for: • First-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations • Use in adult patients with locally-advanced or metastatic EGFR T790M mutation-positive NSCLC Osimertinib is recognised as an innovative therapy in the adjuvant setting and therefore the ADAURA indication has been reviewed as part of Project Orbis. Project Orbis is an FDA OCE initiative with a focus on high-impact cancer drugs; providing a framework for concurrent submission and review of oncology products among international partners. In 2020, the MHRA participated as part of Project Orbis as an observer and became a full participant as of 1st January 2021, however, each country remains fully independent on their final regulatory decision. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Osimertinib (Tagrisso®) monotherapy is **currently** indicated for: 1. The first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations 2. The treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC Osimertinib (Tagrisso®) monotherapy is **anticipated** to be indicated for:[redacted]
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. The company has commercial arrangements that makes osimertinib available to the NHS with a discount for TA653 and TA654 [redacted] The size of the discount is commercial in confidence.
Patient access scheme (if applicable)	Commercial access agreements are currently in place for osimertinib (TA653, TA654). [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; FDA, Food and Drug Administration; 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*

- **NSCLC is a highly prevalent form of lung cancer, accounting for 80–89% of all lung cancers, with high rates of mortality[19-22]**
- **Annually, 18% of patients with NSCLC in England and Wales undergo complete surgical resection, and the annual incidence for completely-resected stage IB–IIIA EGFRm-positive NSCLC eligible for adjuvant therapy is estimated to be 386 patients in England and Wales[19, 23-25]**
- **Despite complete tumour resection, the rates of disease recurrence or death after surgery remain high[4, 26, 27]**
    - After surgery, rates of disease recurrence in resected patients remain unacceptably high, with most patients (68%) experiencing distant metastatic recurrence, at which point treatment is no longer curative[8]
    - CNS metastases are frequent in NSCLC; over 40% of patients who undergo disease recurrence experience this as brain metastasis, which is the most frequent recurrence type[8]
    - Outcomes for patients with brain metastases are especially poor, with a high symptom burden, reduced treatment options, and a median OS of 5−13 months[6, 7, 28]
    - Patients with EGFRm-positive NSCLC are at twice-higher risk of brain metastases than patients with wild-type EGFR[5]
    - The economic burden of NSCLC is higher in metastatic disease than in earlier-stage disease, therefore it is important to improve outcomes for patients earlier in the treatment pathway and reduce the risk of patients recurring with metastatic disease[7, 29]
- **In the UK, approximately 13% of stage IB to 50% of stage IIIA patients receive adjuvant chemotherapy following surgical resection;OBJ however, this provides only an absolute benefit of 5.4% for OS and 5.8% for DFS over 5 years, vs no chemotherapy[4] however, this provides only an absolute benefit of 5.4% for OS and 5.8% for DFS over 5 years, vs no chemotherapy[4]**
    - Following complete resection with or without adjuvant chemotherapy, no further treatment options exist and patients undergo routine surveillance, typically for a period of 5 years
- **With no meaningful innovation in the postoperative adjuvant setting for 20 years, there is a clear unmet need for targeted, efficacious and well-tolerated treatment options for patients with EGFRm-positive NSCLC following complete resection[10, 26, 27]**
    - Adjuvant chemotherapy is offered only to eligible patients (those with high-risk tumour characteristics and good performance status) but provides limited survival benefits vs no chemotherapy;[3, 4] therefore, UK clinicians state that many patients decline adjuvant chemotherapy due to limited perceived value and associated toxicity[18]

- Previous trials of targeted adjuvant first-generation EGFR-TKI therapies showed poor disease control and failed to improve outcomes for patients, meaning EGFR mutations remain an underutilised therapeutic target[11-13]
- Limitations of previous adjuvant EGFR-TKI trials included a treatment duration limited to 2 years, a trial population that included patients with wild-type EGFR, and inclusion of patients without negative margins after surgery[12, 14-16]

- **Osimertinib is anticipated for use as the first targeted therapy after complete tumour resection with or without adjuvant chemotherapy, in patients with EGFRm NSCLC**

B.1.3.1 *Disease overview*

Non-small cell lung cancer (NSCLC) is the most prevalent form of lung cancer in England and Wales, and accounts for 80–89% of all lung cancers.[19, 20] Among the mutations observed in NSCLC tumours, EGFR mutations (EGFRm) are a common type, found in 10% of patients with adenocarcinoma.[30]

Surgical removal of tumours is the preferred treatment for many patients with early-stage NSCLC due to its curative potential.[3, 31-33] Globally, approximately 20–30% of patients present with resectable disease;[34, 35] for other patients, surgical risk factors and inoperable disease make them ineligible.[31, 32] In England and Wales, approximately 18% of patients undergo resection each year.[19] Resection rates range from 10.0–33.3% across individual centres, with potential to increase the rates at the lower end of the scale, due to lower resection rates in the UK than elsewhere in the western world.[19, 33] In an advisory board conducted by AstraZeneca, UK clinicians stated that complete resection is achieved in the majority of patients undergoing surgery.[9]

Despite complete resection with curative intent, many patients with stage IB disease, and the majority with stage II–III disease, experience disease recurrence within approximately 5 years of surgery (during this period, recurrence events occur in 45% with stage IB, 62% with stage II, and 76% with stage III disease).[4] Most post-resection relapses are due to distant recurrence (particularly brain metastases), which therefore contributes a large proportion of treatment failures and deaths in these patients (see Section B.1.3.2.1).[8, 26] Disease recurrence most frequently occurs 18–24 months after surgery (stated by six UK clinicians during interviews).[18] Survival remains poor in the resected population, with survival worsening by increasing disease severity.

Epidemiology

The estimated incidence of lung cancer in England is 41,620 and the incidence of NSCLC is 36,875.[24, 25]. The total incidence of patients in England with EGFRm-positive NSCLC who are stage IB−IIIA, have undergone complete surgical resection, and who are eligible for adjuvant therapy is estimated to be 386, reaching a total of 485 incident patients after 5 years.[23]

B.1.3.2 *Burden to patients and society*

B.1.3.2.1 Clinical burden

Data specific to the EGFRm population around the clinical burden of disease are limited. However, in the broader NSCLC population, early-stage lung cancer is often asymptomatic for many years.[36] When a symptom burden does arise, it includes (but is not limited to) shortness of breath, fatigue, and nausea.[37] Survivors of early-stage lung cancer often experience dyspnoea (60% of survivors).[38] In addition, symptoms of poor mental health are often observed: 20% report clinically significant symptoms of anxiety and approximately 10% report depressive symptoms.[38]

Although surgery is used with curative intent in eligible patients (see Section B.1.3.4.2), many patients subsequently experience recurrence. In stage I–II disease, the 5-year risk of local or distant recurrence following resection is 36%, with the risk of recurrence increasing with disease advancement (from 45% at stage IB to 76% at stage III over an approximate 5-year follow-up, in one meta-analysis).[4, 39] Post-surgical recurrence often occurs rapidly: the median time to local or distant recurrence after resection is reported as 13.9 and 12.5 months, respectively.[40] This was supported by interviews with UK clinicians, who stated that patients are at highest risk of recurrence 18–24 months after surgery, with a low risk of recurrence in the first year after resection and declining recurrence frequency from 2 years after resection.[18]

The added survival benefit of adjuvant chemotherapy is low: a pooled analysis of patients treated with cisplatin-based chemotherapy found that the risk of death is reduced by only 5% compared with patients who receive no chemotherapy.[4] In addition to this limited mortality benefit, many patients will choose not to undergo chemotherapy or are ineligible (Section B.1.3.4.2) and the unmet need for a targeted treatment that improves post-surgical outcomes remains (Section B.1.3.6).

In total, 68% of recurrence events that occur after resection are distant recurrences;[8] treatment thereafter no longer has curative potential, and is instead considered life-extending only. Furthermore, central nervous system (CNS) metastases are common for patients with NSCLC; brain metastases occur in 40−50% of all patients with NSCLC across their disease course, and negatively impact survival (Section B.1.3.3).[7, 41] Among patients with NSCLC, those with EGFRm-positive disease have a two-times significantly higher risk of developing brain metastases as patients with wild-type EGFR (odds ratio [OR]: 1.99; $p<0.05$).[5] Development of brain metastases results in an additional symptom burden: ≥10% of patients with EGFRm NSCLC and brain metastases experience seizures, speech problems, focal neurologic deficits, drowsiness, and memory problems are experienced.[6] The symptom burden often increases during treatment of brain metastases (particularly during whole-brain radiotherapy).[7]

Until the recent reimbursement of osimertinib, EGFR tyrosine kinase inhibitor (TKI) therapies (available to patients with advanced disease; Section B.1.3.4.3) had poor blood-brain barrier penetration;[11, 13, 42] this may have contributed to the poor disease control provided by these therapies in the adjuvant setting.[11, 12] A therapy, such as osimertinib, that can cross the blood-brain barrier and reduce the risk of brain metastases prior to their development would therefore improve survival while reducing

the clinical burden for patients (Section B.1.3.6). The LuCaBis burden of illness study in 831 patients with completely-resected stage IB–IIIA NSCLC in the UK, France, and Germany found brain metastases occurred in 41% of patients with recurrence; other frequent sites of metastasis in patients with disease recurrence included the lungs (occurring in approximately 33% of patients with recurrence), bone (approximately 24%), and liver (approximately 13%).[8]

B.1.3.2.2 Quality of life burden

Patients with NSCLC experience poorer physical health and a slightly poorer quality of life (QoL) than the general population.[38, 43] UK patients with NSCLC who have stable disease and no side effects experience only a small utility decrement: the reported utility value in these patients is 0.84[a], compared with 0.855[a] in the English general population (or 0.856[a] in the UK general population).[44, 45]

Despite the lower burden in early-stage disease (relative to late-stage) and the curative potential of surgery, surgery itself can impact QoL: health-related QoL (HRQoL) is significantly impaired 1 month after surgery before typically returning to preoperative levels at 3 months.[43] However, despite this recovery in HRQoL generally, physical functioning remains below preoperative value at 3 months.[43] Adjuvant chemotherapy causes a HRQoL decline which is temporary, after which patients return to baseline functioning.[46]

Disease progression causes vast decreases in utility, with a decrement of −0.68 reported in patients with progressive disease (a utility value of 0.166 compared to a baseline of stable disease and no side effects).[44] Consequently, the burden is increased by disease advancement, with worse QoL in patients with metastatic disease than in early-stage disease.[47] Interviewed UK clinicians confirmed this, stating that patients with locoregional recurrence experience higher QoL than patients with distant metastases.[18]

Impairments in QoL worsen as disease recurs at either local or distant sites. As with many other cancer types, locoregional recurrence in NSCLC is associated with reduced QoL;[48] however, distant metastatic recurrences impose more substantial QoL impairments. A systematic review of studies on brain metastases found increased symptoms of fatigue, neurological function impairment, motor dysfunction, and reduced concentration, contributing to QoL impairments.[7] Similarly, interviewed UK clinicians reported seizures, migraines, and cognitive impairment in their patients with CNS metastases, resulting in severe deterioration of the patients' mental health.[18] Multiple studies in brain metastases reported deteriorations in European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) scores, and both emotional and social functioning. The declines in HRQoL experienced by patients with brain metastases are significantly faster than for those without brain metastases.[49] Some treatments for brain metastasis (especially brain surgery or radiotherapy) can contribute additional impairment of neurocognitive processes and the ability of patients to carry out routine daily functions.[7] Interviewed UK clinicians confirmed this with their own experience that CNS metastases impose substantial QoL impairments

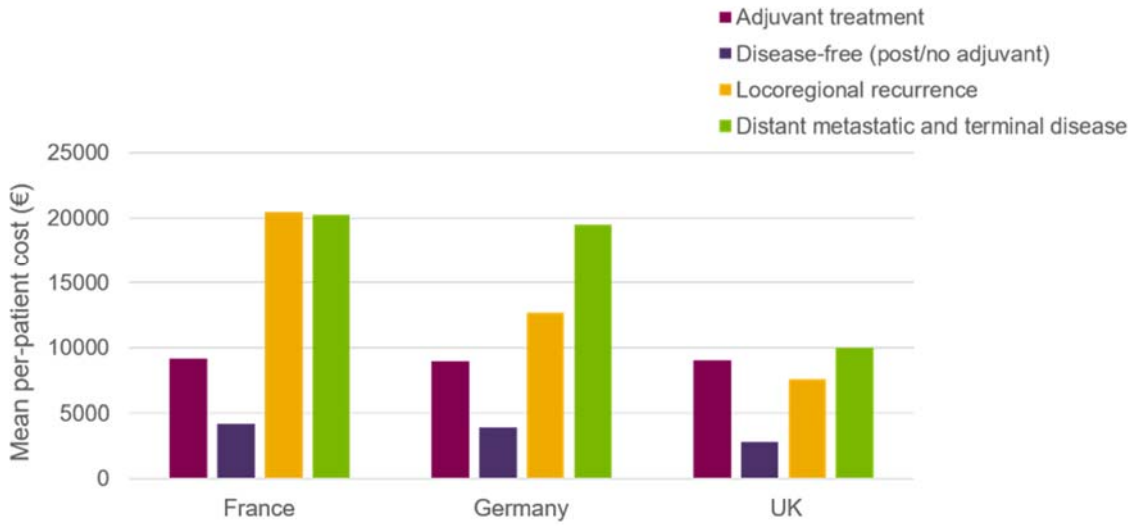
[a] The utility value shown is for all ages.

that are greater than for non-CNS distant metastases, with the treatments for managing CNS metastases further worsening QoL.[18]

B.1.3.2.3 Economic burden

Evidence on the economic burden for resected NSCLC is limited. For completely-resected stage IB–IIIA NSCLC (irrespective of mutation status), mean direct costs per-patient in the UK overall are £6,866 over a median 25 months, predominantly driven by treatment, with substantial additional costs incurred by hospitalisations and specialist appointments.[29] Direct costs are lower for local or regional recurrence than the adjuvant treatment period (due to lower treatment, supportive treatment, and hospitalisation costs). However, direct costs were highest for patients with distant metastatic or terminal disease (who incurred high treatment, hospitalisation, medical visit and diagnostic costs), and lowest in disease-free patients (Figure 1).[29]

Figure 1: Direct mean costs per person associated with NSCLC for the overall follow-up period†, by country and disease phase



† 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.
Abbreviation: NSCLC, non-small cell lung cancer.
Source: adapted from Andreas et al, 2018.[29]

Many patients with resected NSCLC in the UK report absence from work, with some requiring long-term sickness or disability leave or becoming permanently disabled.[29] In total, 17% of patients report a change in employment status due to their disease. Mean per-patient indirect costs for all patients over 25 months are £1,159, although lower during the adjuvant treatment period and more than twice as much for metastatic and terminal disease. Because of the direct, indirect, and out-of-pocket costs of resected NSCLC, the overall annual cost to society is estimated at £267 million.[29]

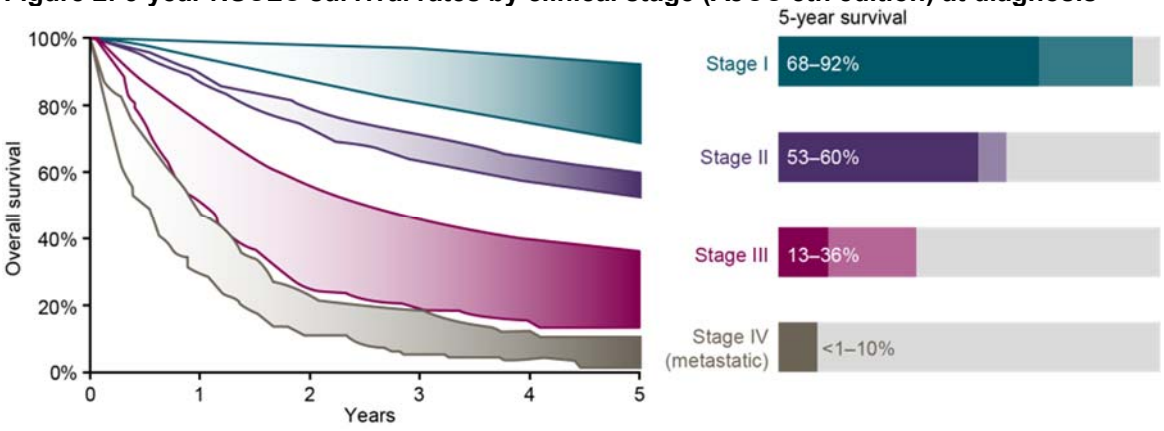
Disease with EGFRm may incur higher costs due to targeted therapies in later lines of treatment, and the increased risk of brain metastases. UK-specific data on costs are limited in this population. However, US data show high healthcare resource utilisation in patients with NSCLC and brain metastases;[7] use of home healthcare, nutrition therapy, physical therapy, rehabilitation and social work services are significantly higher for

patients with EGFRm NSCLC and brain metastases than EGFRm patients with non-brain metastases.[6] When interviewed, UK clinicians confirmed high healthcare resource utilisation in patients with CNS metastases due to the aggressive disease characteristics, including for hospitalisations, surgery and magnetic resonance imaging (MRI) or computed tomography (CT) scans.[18]

B.1.3.3 *Life expectancy*

Despite the curative intent of complete resection with or without adjuvant chemotherapy, NSCLC is associated with a very poor prognosis compared with other cancer types (e.g. colon, rectal or breast cancer).[50-52] The global CONCORD-2 study, which included 26 million patients diagnosed with cancer from 1995–2009, found lung cancer (of which NSCLC is the most prevalent form) to be the most deadly cancer type worldwide.[52] In the UK, age-standardised survival at 5 years for all lung cancers is only 16%.[22] Mortality increases by disease stage, with US registry-derived 5-year survival rates of 68–92% for stage I disease, falling to 13–36% for stage III disease (Figure 2).[53]

Figure 2: 5-year NSCLC survival rates by clinical stage (AJCC 8th edition) at diagnosis



Abbreviations: AJCC, American Joint Committee on Cancer; NSCLC, non-small cell lung cancer.
Source: adapted from Deslypere et al, 2018.[53]

Life expectancy in resectable stage IB–IIIA NSCLC

In the resectable population, recurrence and mortality rates remain high despite surgery with curative intent. After resection, mortality rates range from 38% in stage IB disease to 70% in stage III disease over an approximate 5-year follow-up.[4] Use of adjuvant chemotherapy is intended to mitigate both the mortality and disease recurrence risk, but the actual benefit is unacceptably low. The additional 5-year survival benefit reported by trials ranges from 2−9% (Table 3),[34, 54] with the LACE study reporting 5-year benefits of 5.4% for OS, and 5.8% for DFS, vs no chemotherapy.[4]

Table 3: Overall survival benefit of adjuvant chemotherapy vs no adjuvant chemotherapy

Trial	Patients, n	Stage	5-year survival benefit, %	Hazard ratio (95% CI)	p-value
ALPI	1209	I–IIIA	3	0.96 (0.81, 1.13)	0.589
IALT	1867	I–IIIA	4	0.91 (0.81, 1.02)	0.03
BLT	381	I–IIIA	2	1.02 (0.77, 1.35)	0.90

Trial	Patients, n	Stage	5-year survival benefit, %	Hazard ratio (95% CI)	p-value
ANITA	840	IB–IIIA	9	0.8 (0.66, 0.96)	0.017
LACE	4584	I–IIIA	5	0.89 (0.82, 0.96)	0.004
IGR-MRC	8147	I–IIIA	4	−0.87 (0.81, 0.93)	<0.0000001

Abbreviation: CI, confidence interval.
Sources: Adapted from Le Chevalier, 2010;[34] Lang-Lazdunski, 2013.[54]

Life expectancy upon locoregional disease recurrence

Several factors affect NSCLC prognosis. Locoregional recurrence in NSCLC can mark a reduction in survival outcomes, as with other malignancies.[48] Analysis of the US Surveillance, Epidemiology, and End Results Program (SEER) database (2010–2016) found a 5-year survival in patients with NSCLC diagnosed with local tumour spread of 63%, and 35% for regional tumour spread.[55]

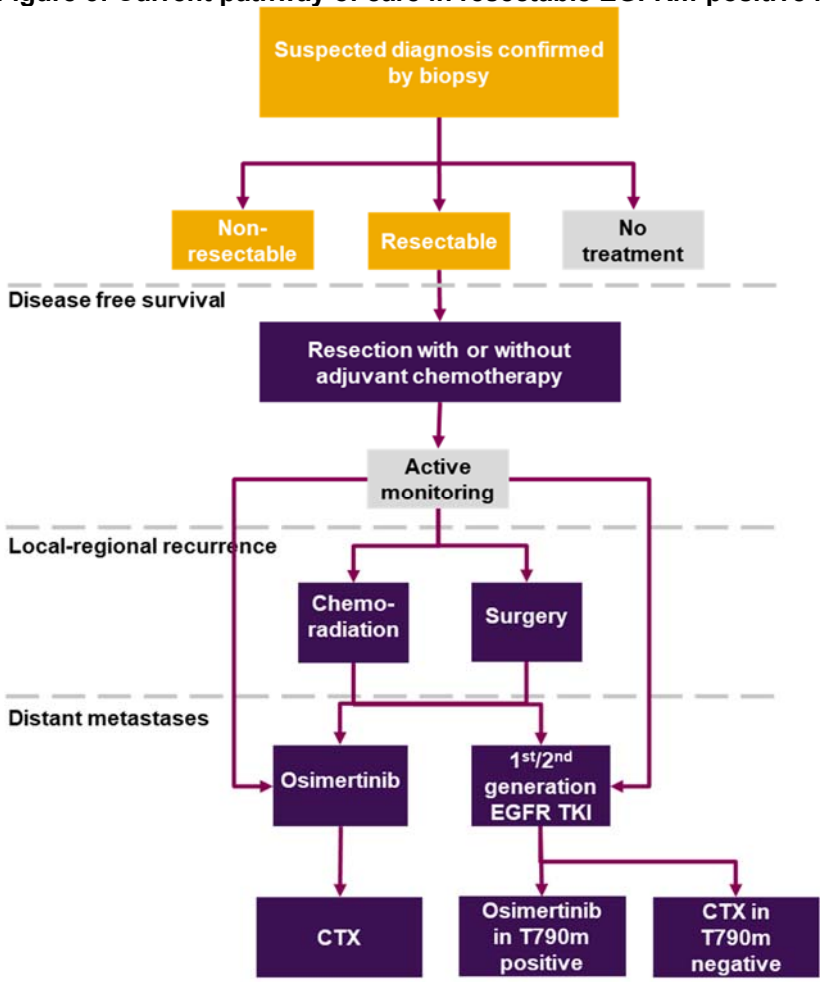
Life expectancy for distant metastatic disease

Patients with distant metastases experience very poor life expectancy, which is worse than for locoregional recurrence: for those with distant metastases of lung cancer in the UK, 5-year survival is 3%.[22] The US SEER database reports a 5-year survival rate of 6.9% for patients with distant metastasis-stage disease.[55] Mortality risk due to lung cancer increases by disease stage, and mortality is especially poor in advanced disease with metastases.[21] Brain metastases are associated with significantly shorter median OS (12 months from metastasis diagnosis) than other metastases (16 months from metastasis diagnosis) in patients with EGFRm-positive disease (p=0.017),[6] and median OS values for brain metastasis range from 5–13 months in Europe, Japan, and the US, regardless of treatment type.[28] Despite a persisting belief that EGFRm-positive NSCLC patients may experience survival benefits in brain metastases,[56] this was not borne out by the findings of a meta-analysis: no significant difference in survival is observed in brain recurrence between patients with and without EGFRm.[5]

B.1.3.4 *Clinical pathway of care*

The current pathway of care for resectable EGFRm-positive NSCLC is shown in Figure 3, and treatment after recurrences is dependent on the type or site of disease recurrence.

Figure 3: Current pathway of care in resectable EGFRm-positive NSCLC



Abbreviations: CTX, chemotherapy; EGFRm, epidermal growth factor receptor mutation; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.
Source: AstraZeneca UK clinician interviews;[18] NICE guideline 122.[3, 57]

B.1.3.4.1 Diagnosis and staging

NICE guidance on NSCLC diagnosis states that suspected lung cancer should be assessed with a chest X-ray.[3] For diagnosis and staging of disease, contrast-enhanced chest CT scans should be offered; liver, adrenal glands and lower neck should be included and ultrasound can be used where the extent of tumour chest wall invasion is uncertain. For peripheral lesions with small lymph nodes (<10 mm) and low probability of nodal malignancy, positron emission tomography (PET)-CT is the preferred investigation after the CT scan. Peripheral or central lesions with large nodes (≥10 mm) should be investigated with node biopsies for node staging, followed by bronchoscopy when node staging does not affect treatment, or surgical mediastinal staging if node staging would affect treatment.[3] PET-CT scans, followed by needle aspirates, are offered in patients with enlarged nodes who might be suited to potentially curative treatment. If suspected, brain metastases should be tested through MRI or contrast-enhanced CT.[3] Genetic testing for EGFR-TK mutations can be performed on biopsied tissue.[58]

Staging of NSCLC is performed according to the American Joint Committee on Cancer (AJCC) staging criteria, based upon primary tumour size and spread, lymph node involvement, and presence of distant metastases. The widely-used seventh-edition AJCC staging criteria was superseded by the eighth edition in 2017, which gives different categorisations related to tumour size, extent of nodal involvement, and metastases.[59] Although some patients will find their disease staging unchanged, 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).[59]

B.1.3.4.2 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).[3, 31-33] Risk of perioperative mortality, as well as lung and cardiovascular function, should be assessed to determine patient suitability for resection.[3] Adjuvant chemotherapy is recommended to reduce the risk of recurrence and spread of disease, and is an option after surgery; preoperative administration is not recommended.[3, 9] Postoperative cisplatin-based chemotherapy is recommended for patients with primary tumour stage 1a–4 (between ≤1 and >7 cm), and no metastases, and with either 1−2 cancerous lymph nodes or tumours ≥4 cm. For postoperative chemotherapy, good PS is required (WHO PS score 0−1; patients with especially poor HRQoL are ineligible).[3] Adjuvant postoperative chemoradiotherapy is suggested for patients with stage IIIA disease and cancer in two nodes who are well enough for the combined treatment.[3]

Following surgery (with or without adjuvant chemotherapy), patients are monitored for disease recurrence over a period of 5 years. Patients who remain disease-free at 5 years are generally considered functionally cured by clinicians, and are discharged from their care.[18] UK clinicians stated that recurrence after 5 years is rare; when it does occur, this is most likely in patients who smoke, leading to development of a new primary tumour.[18]

B.1.3.4.3 Recurrent disease

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

Locoregional recurrence

If initial complete resection is not curative and patients subsequently experience locoregional recurrence, treatment includes a second opportunity for potentially curative therapy; this is chemoradiation (or further surgery for a small proportion of patients).[18] Interviewed UK clinicians asserted that the aim of treatment at this stage is to attempt to provide a cure for patients while disease spread remains manageable.[18]

Disease progression to distant metastases

For patients who experience distant recurrence or progress to distant metastasis, potentially curative therapies are no longer available. Available therapies are instead

used with the aim of extending life expectancy, and treatment recommendations for metastases from NICE include palliation.[3] Distant recurrences in patients with EGFRm NSCLC can be treated with targeted therapies such as the third-generation EGFR-TKI osimertinib, which UK clinicians described as the standard of care in the metastatic setting, and with chemotherapy as the subsequent line of therapy.[18, 60] Alternatively, first- (e.g. erlotinib, gefitinib) or second-generation (e.g. afatinib, dacomitinib) EGFR-TKIs can be administered, followed by chemotherapy, or by osimertinib in patients with T790 mutations.[18, 57, 61-64] Management of brain metastases includes dexamethasone to reduce the symptom burden, and surgery, radiotherapy or systemic therapies.[3, 65] Bone metastases can be treated with single-fraction radiotherapy if palliation is required.[3]

B.1.3.4.4 Osimertinib place in therapy

Osimertinib, with or without chemotherapy, is anticipated to be used as an adjuvant to complete surgical tumour resection in patients with EGFRm-positive NSCLC (Figure 4). This positioning addresses a substantial unmet need among patients who undergo resection, many of whom experience disease recurrence. At present, chemotherapy is used as adjuvant therapy in some patients (approximately 13% at stage IB, increasing to 50% at stage IIIA),[9] but conveys only a 5.4% reduction in risk of death at 5 years.[4] Because not all patients receive adjuvant chemotherapy, many will not experience additional survival benefits (however minimal).[9]

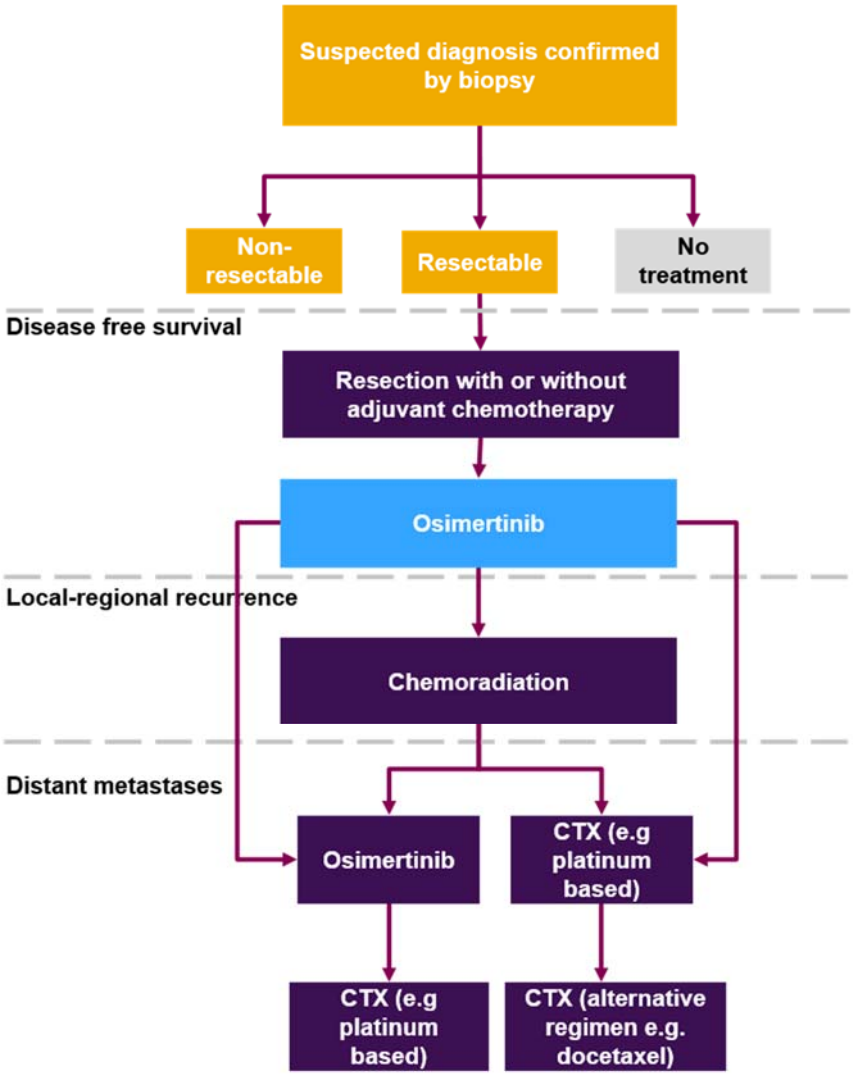
Lack of evidence thus far has led to a lack of targeted therapies in the post-surgical adjuvant setting despite trials of first-generation EGFR-TKIs (gefitinib, erlotinib, and icotinib);[12, 15, 66] consequently, there are currently no specific therapies for EGFRm patients and no advancements in the adjuvant setting for 20 years.[9, 10, 31] Mutation testing for EGFRm-positive disease is recommended by NICE for locally-advanced or metastatic disease to guide treatment pathways for patients ineligible for resection; this is conducted using a central or peripheral tumour biopsy and is often conducted as part of the standard next generation sequencing panel.[58, 67] For early-stage disease, a substantial variation in EGFRm testing is reported by clinicians across the UK, with testing conducted on either pre-surgical biopsies or post-resection samples in the event of relapse.[18] The clinicians interviewed agreed that introduction of a EGFRm-targeted therapy in early-stage disease would provide a rationale to implement early-stage testing.[18] At present, EGFR testing is used further along the treatment pathway or disease course, when patients with EGFRm NSCLC can receive EGFR-TK inhibitors.[58]

Use of a targeted TKI as an adjuvant to potentially curative surgery would represent a step change in the treatment pathway and is expected to significantly improve DFS through reduced recurrence. However, an additional requirement for a new therapy is in the mode of action: previous trials of EGFR-TKIs erlotinib and gefitinib as adjuvant therapies have demonstrated initially promising DFS rates, but few long-term benefits.[11, 12, 14-16] In part, this may result from adept extracranial disease suppression but poor recurrence prevention within the brain, a frequent site of metastasis in EGFRm-positive patients.[11, 12] Osimertinib is the first EGFR-TKI to demonstrate a significant improvement in OS and CNS outcomes in patients with metastatic NSCLC compared with other first- and second-generation EGFR-TKIs, providing further reassurance of the value in the early disease setting (Appendix L.1).[68, 69]

Leveraging the impact of targeted therapies on disease recurrence is predicted to improve long-term outcomes and survival in patients with NSCLC that remain sensitive to curative therapy (i.e. resectable disease) prior to incurably advanced disease. Additionally, a targeted therapy with the ability to pass the blood-brain barrier will reduce brain metastases, leading to better outcomes for patients. As a targeted therapy with blood-brain barrier penetration, osimertinib is expected to fulfil this need. UK clinicians consulted in interviews suggested that they would consider retreatment with osimertinib for patients who successfully completed 3 years of adjuvant treatment with osimertinib and who did not relapse within a year of treatment completion.[18]

However, it is noted that osimertinib as an adjuvant treatment for fully-resected EGFRm-positive NSCLC is an innovative step-change in the treatment pathway and there have been no clinical studies on the use of osimertinib in patients who have received prior osimertinib treatment.Therefore the impact of introducing this highly-efficacious medicine on subsequent treatment options is currently unknown, and the proportion of patients who would be retreated with osimertinib is uncertain. In addition, clinical experts advised that retreatment with other EGFR-TKIs would not be considered as these are generally considered to be less potent and less efficacious versus osimertinib.

Figure 4: Proposed positioning of osimertinib in resectable EGFRm-positive NSCLC



The proposed positioning of 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: CTX, chemotherapy; EGFRm, epidermal growth factor receptor mutation; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.
Source: AstraZeneca UK clinician interviews.[18]

B.1.3.5 *Clinical guidelines*

UK and European guidelines for management of resectable NSCLC (Table 4) are generally in line with NICE guidance;[3, 31, 33] however, ESMO guidelines recommend specific treatment pathways for resectable patients based on disease characteristics.[31]

- Scottish Intercollegiate Guidelines Network (SIGN): Management of lung cancer.[33]
- European Society for Medical Oncology (ESMO): Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.[31]

Table 4: Guidelines for surgery and adjuvant therapies in resectable disease

SIGN 137[33]	ESMO 2017[31]
• 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 I–II** • 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 • Comorbidities, time from surgery and postoperative recovery should be considered for adjuvant chemotherapy • Two-drug cisplatin combinations are preferred for adjuvant therapy • Targeted agents (e.g. EGFRm-specific) are not currently recommended for adjuvant therapy **Stage III** • Disease should be considered resectable in cases of single station N2 disease, T4N0 tumours, or where nodal down-staging has followed induction therapy • Adjuvant chemotherapy should be offered for resected stage III • Where N2 disease is only documented intra-operatively, treat with surgery followed by adjuvant chemotherapy • Where single-station N2 disease is apparent, treat with surgery followed by adjuvant chemotherapy or induction chemotherapy/chemoradiotherapy followed by surgery • Platinum-based chemotherapy (preferably cisplatin) is recommended • In multistation N2 or N3, concurrent definitive chemoradiotherapy is preferred; role of surgery can be considered • In resectable superior sulcus tumours, concurrent chemoradiotherapy induction followed by definitive surgery is preferred

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: SIGN 137, 2014;[33] Postmus et al, 2017.[31]

B.1.3.6 *Issues relating to current clinical practice*

Rates of mortality and disease recurrence among patients with resectable NSCLC are high, despite complete tumour resection, and worsen at later disease stages.[4] Recurrent disease may be locoregional or distant, but is frequently distant recurrence including within the brain (brain metastasis) in patients with NSCLC;[7, 28, 70] EGFRm is associated with significantly higher risk of brain metastasis compared with wild-type EGFR NSCLC.[5]

Adjuvant chemotherapy after complete resection is an established treatment for other cancers (such as breast and colon) and is used in NSCLC with the intent to reduce recurrence and death, improving the cure rate of surgery.[27] Despite the intent to improve surgical outcomes, these improvements are minor. Use of adjuvant chemotherapy was first trialled 50–60 years ago, but did not immediately become standard of care due to unclear clinical benefit.[26, 27] More recently, pooled analyses have confirmed a 5-year survival benefit of only 5.4% compared with no chemotherapy.[4] The limited benefit and side effects of adjuvant chemotherapy mean that only a proportion of those eligible receive it.[8]

There has been no meaningful innovation in the postoperative adjuvant setting for 20 years.[10] Although the benefit provided is limited, chemotherapy remains the only option to improve survival outcomes, despite high mortality after resection. No targeted therapies (including those specific to the EGFRm population) are currently available for patients in the UK as adjuvant therapy for NSCLC following complete resection.[3] Treatment options for patients with resectable EGFRm NSCLC are therefore limited to those generally available and non-targeted, and these mutations offer an underutilised therapeutic target to increase disease-free survival after surgery.

Unmet need

Despite the potential of targeted therapy, previous clinical trials of adjuvant early generation EGFR-TKIs have shown high rates of brain metastases, suggesting poor disease control due to poor blood-brain barrier penetration.[11-13] There is therefore a clear unmet medical need for a targeted, high efficacy, well-tolerated treatment that crosses the blood-brain barrier to prevent CNS metastases and improve survival following surgery.

B.1.4 *Equality considerations*

No equality considerations have been identified.

B.2. Clinical effectiveness

- **The clinical evidence demonstrates that adjuvant osimertinib with or without postoperative chemotherapy results in clinically significant, unprecedented improvements in DFS and a significantly lower risk of CNS recurrence or death compared with placebo[17]**
    - Evidence comes from an interim analysis of data from the Phase III, randomised, double-blind, multicentre ADAURA study, which was unblinded at a trial level[b] two years early due to overwhelming efficacy[17]
    - ADAURA evaluates the efficacy and safety of osimertinib (with or without chemotherapy) vs placebo (with or without chemotherapy) as adjuvant therapy following complete resection in adult patients with NSCLC[17]
    - A final analysis is planned for two years after this interim data cut[17]
- **For the primary efficacy outcome of DFS, osimertinib demonstrated a significant 80% reduction in risk of recurrence or death vs placebo in the overall trial population (hazard ratio [HR]: 0.20; 99.12% confidence interval [CI]: 0.14, 0.30; p<0.001)[17]**
    - In the stage II–IIIA population, osimertinib demonstrated a significant 83% reduction in risk of recurrence or death vs placebo (HR: 0.17; 99.06% CI: 0.11, 0.26; p<0.001)[17]
    - The DFS benefit of osimertinib was consistent across all patient subgroups, including by disease stage and prior adjuvant chemotherapy[17]
- **At 24 months, the DFS rate in the overall population was 89% in the osimertinib arm vs 52% in the placebo arm[17]**
    - In the stage II–IIIA population at 24 months, the DFS rate was 90% in the osimertinib arm vs 44% in the placebo arm[17]
    - [redacted]
- **A clinically meaningful, significant 82% reduction in risk of CNS recurrence or death in the overall population was observed with osimertinib vs placebo (HR: 0.18; 95% CI: 0.10, 0.33; p<0.0001; analysis was post hoc)[17, 72]**
    - [redacted]
- **In patients who had a disease recurrence or progression, the majority experienced locoregional recurrence when treated with osimertinib, compared with a majority who experienced distant recurrence in the placebo group [17]**

[b] Patients and investigators remain unaware of study group assignments.[17]

- **OS data were immature at the time of the interim data cut; however, a numerical benefit was observed in the overall population with osimertinib vs placebo (2.7% and 5.8% of patients, respectively, had died)[17, 71]**
    - In the stage II–IIIA population, 3.4% of patients with osimertinib and 7.2% with placebo had died (HR: 0.40; 99.98% CI: 0.09, 1.83; not statistically significant)[17]
- **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[17]**
    - The proportion of patients undergoing dose modifications and discontinuations with osimertinib was low[17]
    - Interstitial lung disease (ILD) events were mild or moderate in severity and no meaningful differences in cardiac events were observed between groups[17]

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-positive 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-positive 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[17, 71] (summarised in Table 5 and reported in detail in this submission).

Additional supporting evidence in the submission comes from the FLAURA study and the CancerLinQ database (evidence not included in the clinical SLR) which are used to support the economic modelling and are presented in Appendix L. In particular, the FLAURA study reports clinical evidence for osimertinib at later stage of the disease pathway and therefore also provides key insights regarding the efficacy of osimertinib for the treatment of patients with NSCLC.

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 5). A more detailed trial overview is presented in Table 6.

Table 5: List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study ref(s)	Refs identified but not used further	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)	Wu et al, 2020[17] (not identified in clinical SLR as published more recently than the search date) Tsuboi et al, 2020[72] (not identified in clinical SLR as published more recently than the search date) CSR, interim analysis[71]	EUCTR trial EUCTR2015-000662-65-ES, 2015[73] Herbst et al, 2020[74] Clinicaltrials.gov, 2015[75] Tsuboi et al, 2019[76] Wu et al, 2018[77]	No

Abbreviations: 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 6: Clinical effectiveness evidence

Study	ADAURA				
Study design	Phase III, randomised, double-blind, placebo-controlled, multicentre study (ongoing)				
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.

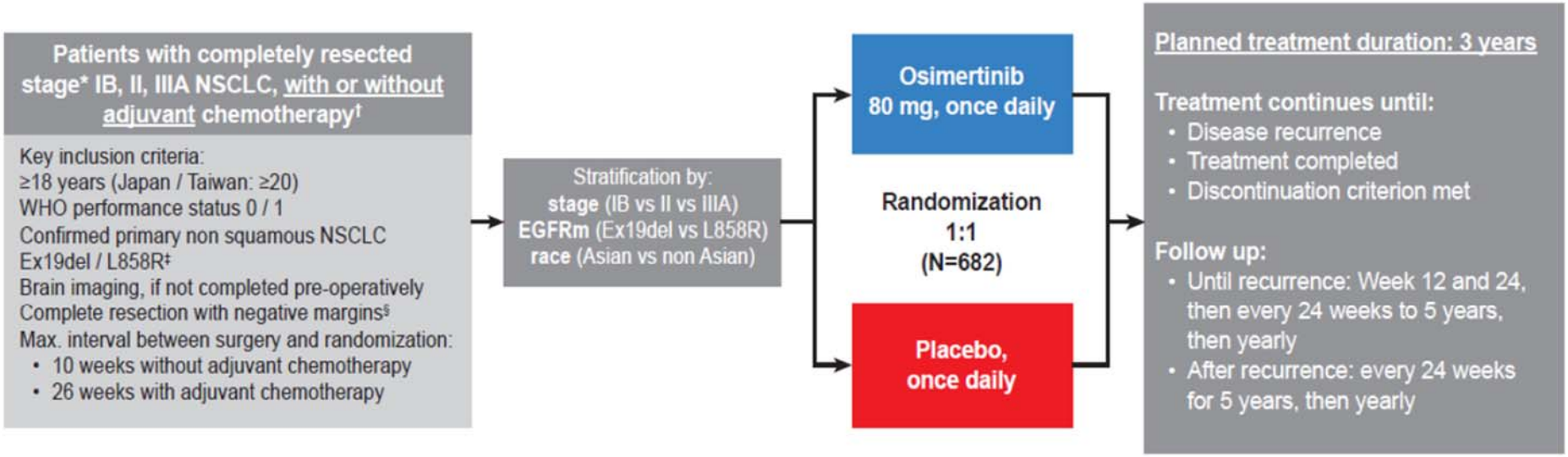
B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

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

ADAURA (NCT02511106) is a Phase III, 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-positive NSCLC.

After the planned review by the Independent Data Monitoring Committee (IDMC) in April 2020, the committee recommended that the trial be unblinded two years early after determination of overwhelming efficacy with osimertinib.[1] The results of this interim analysis are reported here and form the basis of this submission. The trial design is summarised in Figure 5 and Table 7, with inclusion and exclusion criteria summarised in Table 8.

Figure 5: 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.[17]

Table 7: Summary of ADAURA methodology

Trial number (acronym)	**ADAURA**
Settings and locations	[redacted] 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	For the planned analysis, the primary study population was all patients with stage II–IIIA disease. This represented a subset of the overall ADAURA study population, which included patients with stage IB–IIIA NSCLC. The overall population is the main population of relevance to the current submission. 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). The final analysis of OS will be conducted when ~94 deaths have been observed in the stage II–IIIA population (approximately 20% maturity). A final exploratory analysis of DFS in the stage II–IIIA population will be conducted once approximately 247 DFS events have occurred in this subset. An exploratory analysis of DFS will be conducted in the overall population once there has been approximately 247 DFS events in the stage II–IIIA population and approximately 70 DFS events in the overall population.
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: 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.
Source: Wu et al, 2020;[17] clinicaltrials.gov.[75]

Table 8: 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;
Sources: Wu et al, 2020.[17]

B.2.3.2 *Patient disposition (ADAURA)*

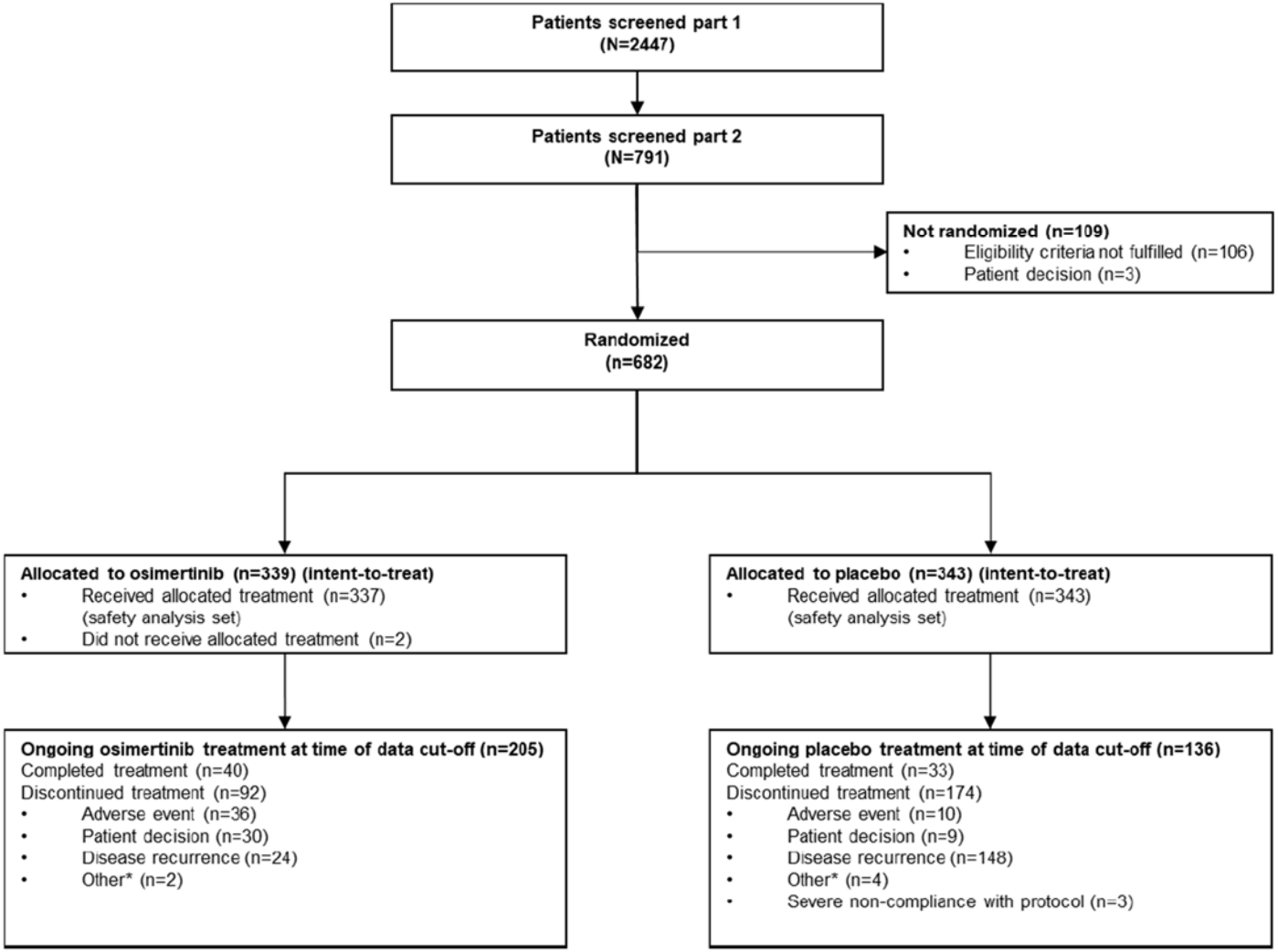
Patients were enrolled at [redacted] in 24 countries across Europe, Asia-Pacific, North America, and South America.[71, 75] In total, 682 patients were randomised (339 to osimertinib and 343 to placebo) and of these, 337 and 343 patients in the osimertinib and placebo arms, respectively, received their allocated treatment (Figure 6).[17]

At the time of the interim data cut, [redacted][71]
73 patients had completed treatment (40 [12%] with osimertinib and 33 [10%] with placebo) and 341 patients were still undergoing treatment (205 with osimertinib and 136 with placebo).[17] The median duration of treatment exposure was 22.5 months in the osimertinib arm and 18.7 months in the placebo arm.[17]

In total, 92 patients in the osimertinib arm and 174 patients in the placebo arm discontinued treatment. In the osimertinib arm, this was most frequently due to adverse events (AEs; 36 patients), followed by patient decision (30 patients), disease recurrence

(24 patients), or other reasons (2 patients).[17] In the placebo arm, discontinuations were most frequently due to disease recurrence (148 patients) followed by AEs (10 patients), patient decision (9 patients), other reasons (4 patients) and protocol non-compliance (3 patients).[17]

Figure 6: Patient disposition in ADAURA



*Any reason not specifically recorded.
Wu et al, 2020.[17]

B.2.3.3 *Patient baseline characteristics (ADAURA)*

From November 2015 to February 2019, 682 patients were randomised, 339 to osimertinib and 343 to placebo.[17] Key patient demographics and characteristics at baseline are summarised in Table 9. The majority (>60%) of patients were Asian, and approximately a third of each cohort was stage IB/II/IIIA, with disease stage balanced across treatment arms.[17] PS was balanced between treatment arms; most patients had PS 0 at baseline, as expected.[17] The treatment arms were generally well matched at baseline, and disease characteristics between the two arms were similar (Table 10).[17]

Table 9: 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 Asian Other Missing	[redacted]	[redacted]
Smoking status, n (%) Never Former Current	[redacted]	[redacted]
Median body mass index, kg/m^2 (range)	[redacted]	[redacted]

Abbreviation: FAS, full analysis set.
Sources: ADAURA CSR;[71] Wu et al, 2020.[17]

Table 10: Key disease characteristics in ADAURA

Characteristic (FAS)	Osimertinib N=339	Placebo N=343
WHO performance status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
AJCC stage at diagnosis, n (%)		
IB	[redacted]	[redacted]
IIA	[redacted]	[redacted]
IIB	[redacted]	[redacted]
IIIA	[redacted]	[redacted]
EGFR mutations, n (%)		
Exon 19 deletions	[redacted]	[redacted]
L858R	[redacted]	[redacted]
Histology type, n (%)		
Adenocarcinoma		
Acinar	[redacted]	[redacted]
Papillary, malignant	[redacted]	[redacted]
Malignant	[redacted]	[redacted]
Bronchiolo-alveolar	[redacted]	[redacted]
Solid with mucous formation	[redacted]	[redacted]
Bronchial gland carcinoma (NOS)	[redacted]	[redacted]
Carcinoma, adenosquamous, malignant	[redacted]	[redacted]
Other	[redacted]	[redacted]
Lung cancer resection type, n (%)		
Lobectomy	[redacted]	[redacted]
Sleeve resection	[redacted]	[redacted]
Bilobectomy	[redacted]	[redacted]
Pneumonectomy	[redacted]	[redacted]
Regional lymph nodes, %		
N0	[redacted]	[redacted]
N1	[redacted]	[redacted]
N2	[redacted]	[redacted]
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)

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,[17] ADAURA CSR.[71]

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 a two-sided α-level of 5% for the comparison of osimertinib with placebo (with or without adjuvant chemotherapy [representing current clinical management alongside active monitoring]). The interim analysis presented in this submission 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 for the interim analysis.[78]

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[c] 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[d] in the stage II–IIIA[c] population and OS[d] in the overall population with the test mass split between first and second analyses

[c] According to staging at diagnosis.
[d] The trial was not powered for OS.

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 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 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. 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 11.

Table 11: 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 than in the osimertinib arm, but this was driven by a higher rate of disease recurrence in the placebo arm.
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.
Source: ADAURA CSR;[71] Wu et al, 2020.[17]

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

B.2.6.1 *ADAURA Study*

The presented results are from the interim analysis from the data cut-off of 17 January 2020. At the time of the cut-off, data maturity was 33.2% (from the primary endpoint of disease-free survival). This cut-off was performed earlier than the planned cut-off at 50% maturity due to a recommendation of overwhelming efficacy by the IDMC.[1, 17] An additional efficacy analysis will be conducted approximately 2 years after the interim data cut-off ([redacted]).

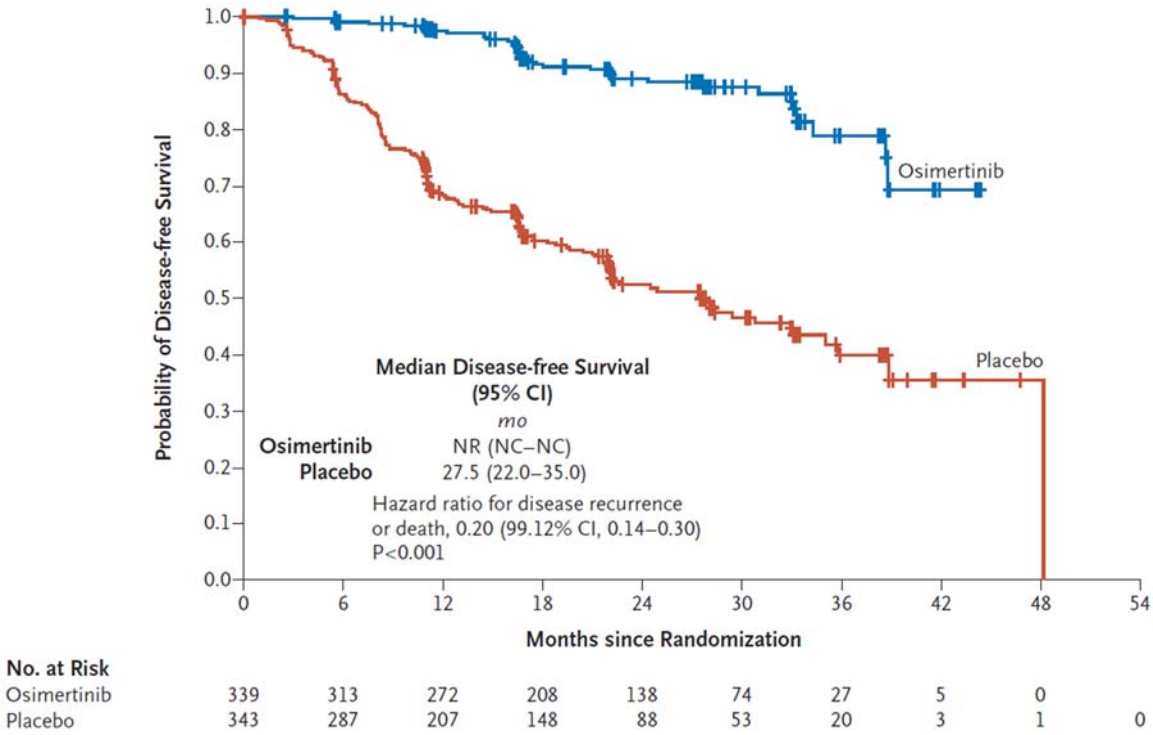
For the planned ADAURA analysis, the primary study population was patients with stage II–IIIA disease. This represented a subset of the overall ADAURA study population, which included patients with stage IB–IIIA NSCLC. For the current submission, the overall population is the main population of relevance, and data are therefore presented first.

B.2.6.1.1 Primary efficacy outcome – disease-free survival

In the overall population, treatment with osimertinib resulted in significantly longer DFS, with an 80% lower risk of disease recurrence or death vs placebo (HR: 0.20; 99.12% CI: 0.14, 0.30; p<0.001) (Figure 7).[17]

Median DFS was not reached with osimertinib and was 27.5 months in the placebo group.

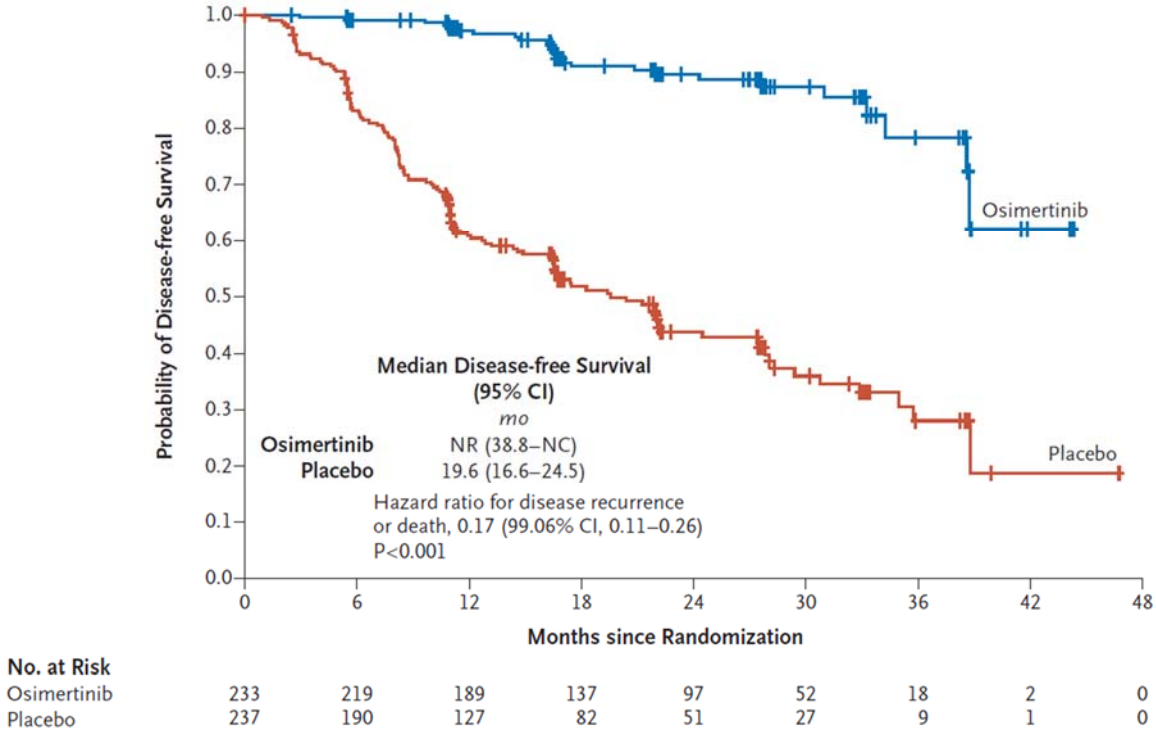
Figure 7: Kaplan-Meier plot of DFS in ADAURA – interim analysis in overall population



Abbreviations: CI, confidence interval; DFS, disease-free survival; NC, not calculable; NR, not reached.
Source: Wu et al, 2020.[17]

Treatment with osimertinib significantly improved DFS in the stage II–IIIA population, reducing the risk of disease recurrence or death by 83% vs placebo (HR: 0.17; 99.06% CI: 0.11, 0.26; p<0.001) (Figure 8).[17] The median DFS was not reached with osimertinib and 19.6 months with placebo.

Figure 8: Kaplan-Meier plot of DFS in ADAURA – interim analysis in stage II–IIIA population

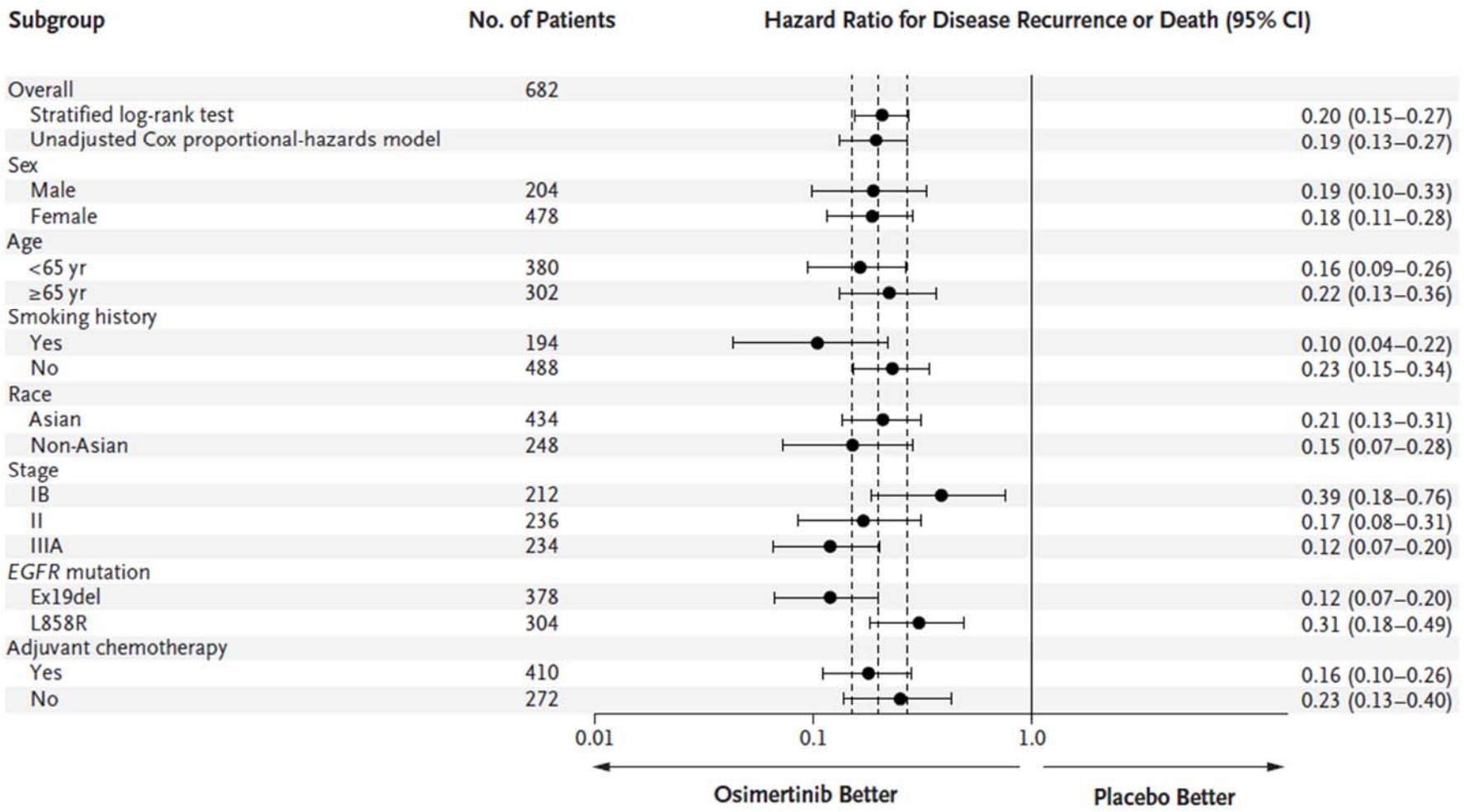


Abbreviations: CI, confidence interval; DFS, disease-free survival; NC, not calculable; NR, not reached.
Source: Wu et al, 2020.[17]

Subgroup analysis

The DFS benefit observed with osimertinib was observed across all pre-defined subgroups, providing confidence in applicability of the results to patients in the UK (Figure 9).[17] Subgroups across which the benefit was observed included male/female sex, disease stages IB, II, and IIIA, and patients who had or had not received adjuvant chemotherapy.

Figure 9: Subgroup analysis of DFS in ADAURA – interim analysis in overall population



Abbreviations: CI, confidence interval; DFS, disease-free survival; EGFR, epidermal growth factor receptor.
Source: Wu et al, 2020.[17]

Sensitivity analysis

[redacted]

Disease-free survival rate

[redacted]

In the overall population at 24 months, 89% of patients in the osimertinib group were alive and disease-free, vs 52% with placebo.[17] In the stage II–IIIA population at 24 months, 90% of patients in the osimertinib group were alive and disease-free, vs 44% with placebo.[17]

Table 12: DFS by timepoint in ADAURA

% (95% CI)	Osimertinib	Placebo
Overall population		
N	339	343
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	89.1 (84.5, 92.4)	52.4 (46.4, 58.1)
36 months	[redacted]	[redacted]
Stage II–IIIA population		
N	233	237
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	89.5 (84.0, 93.2)	43.6 (36.5, 50.6)
36 months	[redacted]	[redacted]

Abbreviation: CI, confidence interval.
Source: ADAURA CSR;[71] Wu et al, 2020.[17]

By disease stage, the proportions of patients alive and disease-free at 24 months in the osimertinib and placebo arms were: 88% and 71%, respectively, for stage IB patients (HR: 0.39); 91% and 56%, respectively, for stage II patients (HR: 0.17); 88% and 32%, respectively, for stage IIIA patients (HR: 0.12).[17]

By adjuvant chemotherapy use, the proportions of patients alive and disease-free at 24 months in the osimertinib and placebo arms were: 89% and 49%, respectively, of patients who received adjuvant chemotherapy (HR: 0.16); and 89% and 58%, respectively, of patients who did not receive adjuvant chemotherapy (HR: 0.23).[17]

B.2.6.1.2 Secondary efficacy outcomes

Type and timing of disease recurrence

Recurrence events occurred in a lower proportion of patients in the osimertinib arm than in the placebo arm (11% and 46%, respectively). Of the patients with recurrence events in the osimertinib arm, local or regional recurrence only occurred in a higher proportion of patients than distant recurrences (7% and 3%, respectively). However, with placebo, distant metastases were the most frequently-observed type (18% locoregional and 23% distant; Table 13).[17]

[redacted] Recurrence in the CNS was reported in 5 patients with osimertinib vs 34 patients with placebo (see CNS recurrence (post hoc analysis)).

[redacted]

Table 13: Type of disease recurrence

n (%)	Osimertinib	Placebo
Overall population		
N	339	343
Disease recurrence†	37 (10.9)	157 (45.8)
Local/regional only	23 (6.8)	61 (17.8)
Distant only	10 (2.9)	78 (22.7)
Local/regional and distant	4 (1.2)	18 (5.2)
Stage II–IIIA population		
N	233	237
Disease recurrence†	[redacted]	[redacted]
Local/regional only	[redacted]	[redacted]
Distant only	[redacted]	[redacted]
Local/regional and distant	[redacted]	[redacted]

† DFS events not occurring within window of two scheduled visits of the last evaluable assessment were censored.
Abbreviation: CI, confidence interval.
Sources: ADAURA CSR,[71] Wu et al, 2020.[17]

Overall survival

At the time of the data cut-off, OS data were not considered mature (4.3% maturity) and most patients were still in the survival follow-up [redacted][17, 71] in total, 9 patients in the osimertinib arm and 20 patients in the placebo arm had died by the interim cut (2.7% and 5.8%, respectively).[17]

[redacted]

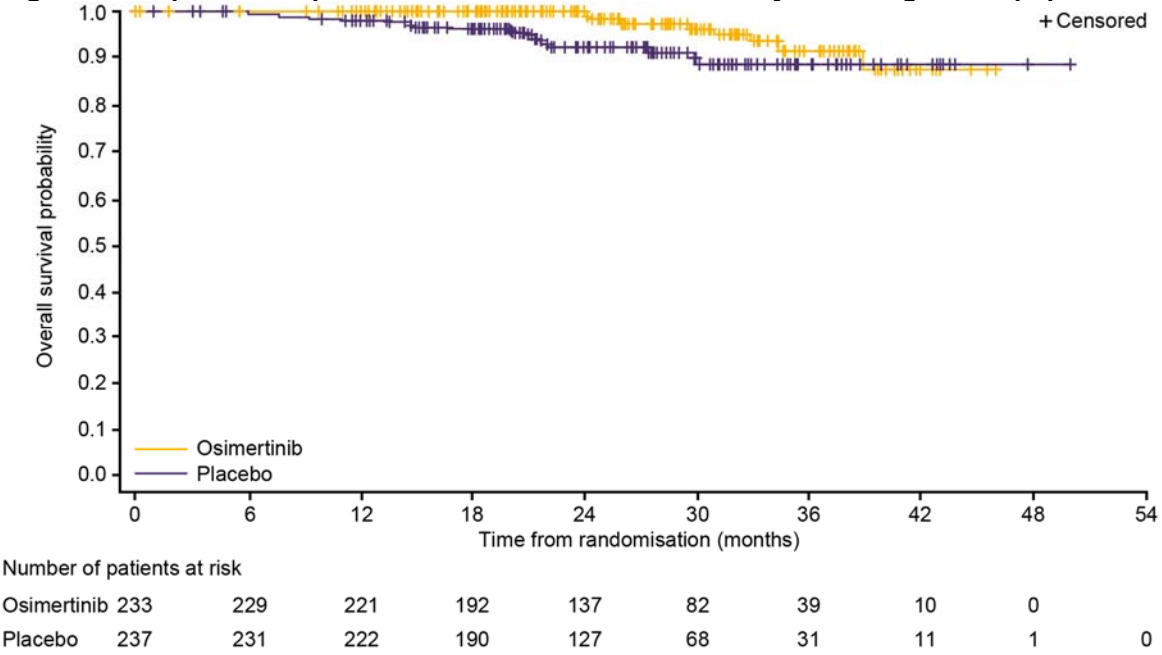
In the stage II–IIIA population (5.3% data maturity), 3.4% of patients with osimertinib and 7.2% with placebo had died by the interim cut (HR: 0.40; 99.98% CI: 0.09, 1.83; [redacted]), which did not reach the required threshold for statistical significance**Error! Bookmark not defined.** (Figure 11).[17, 71] Median OS was not calculable in both treatment arms.[17]

Figure 10: Kaplan-Meier plot of OS in ADAURA – interim analysis in overall population

[redacted]

Abbreviation: OS, overall survival.
Source: ADAURA CSR.[71]

Figure 11: Kaplan-Meier plot of OS in ADAURA – interim analysis in stage II–IIIa population



Number of patients at risk

Osimertinib	233	229	221	192	137	82	39	10	0
Placebo	237	231	222	190	127	68	31	11	1	0

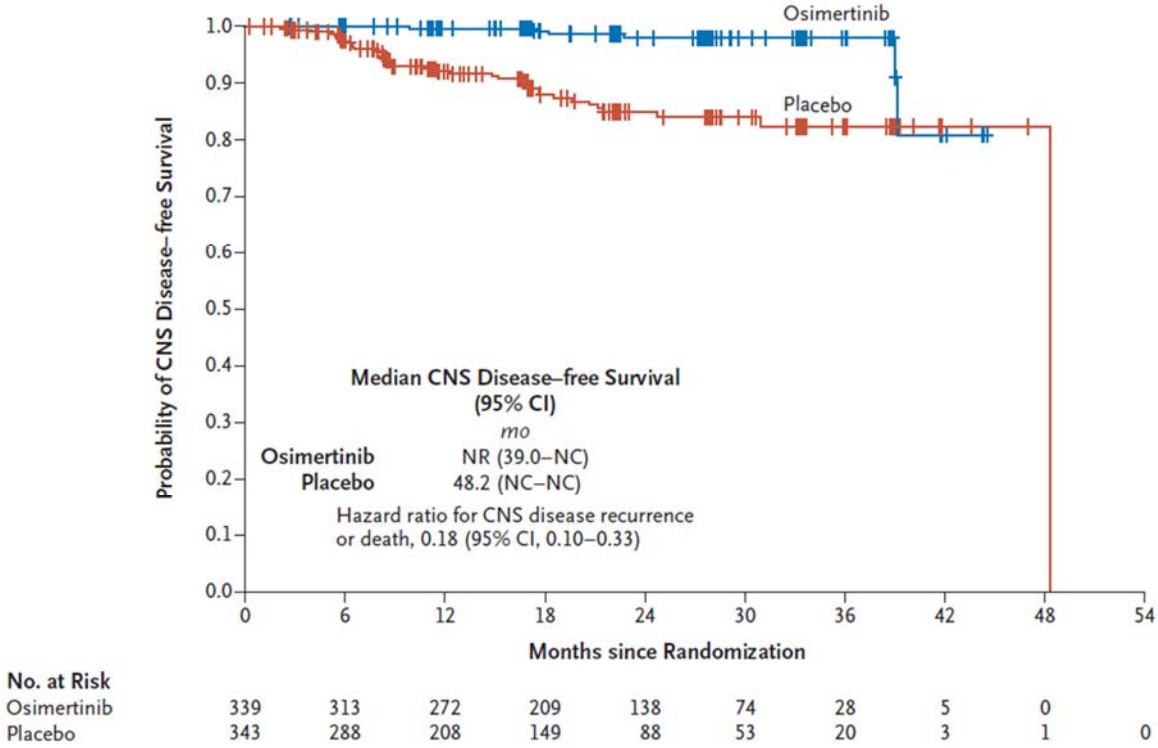
Abbreviation: OS, overall survival.
Source: Wu et al 2020.[17]

CNS recurrence (post hoc analysis)

A clinically meaningful significantly lower risk of CNS recurrence or death was observed with osimertinib compared with placebo: the HR for CNS DFS was 0.18 (95% CI: 0.10, 0.33; p<0.0001) in the overall population, [redacted], indicating an 82% and [redacted] reduction, respectively, in the osimertinib arm compared with placebo.[71, 72]

In the overall population, the proportion of patients experiencing CNS events was numerically lower with osimertinib (4 patients [1.2%]) vs placebo (33 patients [9.6%]).[17] [redacted]

Figure 12: Kaplan-Meier plot of CNS DFS in ADAURA study; overall population, post hoc interim analysis



Abbreviations: CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; NC, not calculable; NR, not reached.
Source: Wu et al, 2020.[17]

Table 14: Summary of CNS recurrence or death

n (%)	Osimertinib	Placebo
Overall population		
N	339	343
Any event	6 (1.8)	39 (11.4)
CNS recurrence	4 (1.2)	33 (9.6)
Death	2 (0.6)	6 (1.7)
Hazard ratio (95% CI)	0.18 (0.10, 0.33)	
2-sided p-value	<0.0001	
Stage II–IIIA population		
N	233	237
Any event	[redacted]	[redacted]
CNS recurrence	[redacted]	[redacted]
Death	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
2-sided p-value	[redacted]	

† DFS events not occurring within window of two scheduled visits of the last evaluable assessment were censored.
Abbreviation: CI, confidence interval.
Sources: ADAURA CSR;[71] Tsuboi et al, 2020.[72]

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 adjuvant-stage patients 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.[71]

[redacted]

[redacted]

B.2.6.1.4 Conclusion

In the randomised, double-blind, Phase III ADAURA trial, osimertinib as adjuvant therapy to complete resection, with or without chemotherapy, resulted in a significant and clinically meaningful DFS benefit compared with placebo.[17] Use of osimertinib in this setting represents a substantial shift in the traditional treatment pathway, as the first targeted therapy for patients with EGFRm NSCLC (Section B.1.3.4).

Adjuvant osimertinib demonstrated a statistically significant and clinically meaningful 80% reduction in disease recurrence or death for the overall population compared with placebo (HR: 0.20; 99.12% CI: 0.14, 0.30; p<0.001), and a significant 83% reduction in risk of recurrence or death in patients with stage II–IIIA disease at the data cut-off (HR: 0.17; 99.06% CI: 0.11, 0.26; p<0.001).[17] [redacted][71] and the benefit was observed consistently across all disease stages and irrespective of adjuvant chemotherapy use.[17]

At 24 months, the DFS rate in the overall population was 89% in the osimertinib arm, compared with 52% in the placebo arm; the 24-month DFS rate in the stage II–IIIA population was 90% in the osimertinib arm compared with 44% in the placebo arm.[17] [redacted][71]

Fewer recurrence events occurred in the osimertinib arm than in the placebo arm (11% and 46%, respectively). For patients who experienced recurrence, this was more frequently locoregional recurrence in the osimertinib arm, but more frequently distant recurrence in the placebo arm.[17]

An unprecedented and highly clinically meaningful, significant 82% reduction in risk of CNS recurrence or death was observed with osimertinib vs placebo (HR: 0.18; 95% CI: 0.10, 0.33; p<0.0001) in the overall population,[72] [redacted].[71] In total, the proportions of patients experiencing CNS events with osimertinib and placebo were 1.2% and 9.6%, respectively, in the overall population,[17] [redacted].[71]

OS data were immature at the time of the interim data cut, but indicated a trend favouring osimertinib (statistical significance will be assessed in the planned final OS analysis at 20% data maturity).[17, 71] The data immaturity at this interim cut are as expected, and align with statements by UK clinicians in interviews that most relapses are expected to occur at 18–24 months (as treatment exposure in the placebo arm was 18.7 months, most relapses and subsequent deaths would be expected later).[18] In the overall population, 2.7% in the osimertinib arm and 5.8% in the placebo arm had died by the data cut-off; in the stage II–IIIA population, 3.4% of patients with osimertinib and

7.2% with placebo had died (HR: 0.40; 99.98% CI: 0.09, 1.83; not statistically significant).[17]

[redacted]

B.2.7 *Subgroup analysis*

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

B.2.8 *Meta-analysis*

No meta-analysis was performed for osimertinib as an adjuvant therapy to complete surgical resection because the ADAURA RCT was the only relevant clinical trial identified (Section B.2.2).

B.2.9 *Indirect and mixed treatment comparisons*

Osimertinib has been studied in the Phase III ADAURA trial where osimertinib with or without chemotherapy is compared with placebo (with or without chemotherapy). Established clinical management following resection in the UK reflects the use of active monitoring with or without adjuvant chemotherapy, and therefore the appropriate comparator for osimertinib is captured in the ADAURA head-to-head trial. In addition, established clinical management without osimertinib is referenced in the NICE scope as the appropriate comparator, and as a result, performing an indirect comparison is not necessary for this submission.

B.2.10 *Adverse reactions*

B.2.10.1 *ADAURA*

B.2.10.1.1 Exposure

The median duration of total treatment exposure in the overall population was 22.5 months (range: 0–38) in the osimertinib group and 18.7 months (range: 0–36) in the placebo group.[17] This is consistent with a longer median DFS in the osimertinib arm and was limited by the analysis being performed earlier than planned (median follow up for the primary endpoint was 22.1 months in the osimertinib arm).[17, 71]

The proportions of patients who received adjuvant platinum-based chemotherapy were similar in the two treatment groups, with ~25% of patients with stage IB disease, ~70% of patients with stage II disease, and ~80% of patients with stage IIIA disease receiving adjuvant chemotherapy.[17] These proportions are higher than published rates of adjuvant chemotherapy in the UK (for patients diagnosed 2009–2011);[8] however, the rates of adjuvant chemotherapy use in ADAURA were considered reflective of clinical practice in England by clinicians consulted during an advisory board.[9]

B.2.10.1.2 Adverse event overview

In total, 98% of patients in the osimertinib group and 89% in the placebo group reported ≥1 AE during the trial (Table 15).[17] Of these, serious AEs (SAEs) were reported by 16% and 12% of patients treated with osimertinib and placebo, respectively.[17]

[redacted]

[redacted][71] Only one death occurred due to an AE (pulmonary embolism); this occurred in the placebo group.[17] Dose modifications and treatment discontinuations due to osimertinib were low, and no new safety concerns were reported.[17]

The most common AEs (reported by ≥10% of patients in either treatment group) are shown in Table 16. AEs reported by ≥10% more patients with osimertinib than placebo included diarrhoea, paronychia, dry skin, pruritis, and stomatitis.[17] Adverse events of special interest included ILD and cardiac AEs. Reported ILD events all occurred in the osimertinib arm and all events were mild or moderate in severity, with one event reported as serious.[17] No meaningful differences in cardiac events were observed between groups; cardiac events were reported in 16 (5%) patients treated with osimertinib and 10 (3%) patients treated with placebo, with one serious event occurring in the osimertinib group.[17]

Table 15: Summary of AEs in ADAURA

AEs, n (%)	Osimertinib (N=337)	Placebo (N=343)
Any AE	329 (98)	306 (89)
AEs considered causally-related to treatment†	[redacted]	[redacted]
AEs of CTCAE Grade 3 or higher considered causally-related to treatment	[redacted]	[redacted]
Any AE with outcome of death	0	1 (<1)
AEs with outcome of death considered causally-related to treatment†	[redacted]	[redacted]
Any SAE	54 (16)	42 (12)
SAEs considered causally reported to treatment†	[redacted]	[redacted]
Change in treatment/trial continuation due to AEs		
Trial regimen discontinuation	37 (11)	10 (3)
Dose interruption	80 (24)	37 (11)
Dose reduction	29 (9)	3 (1)

† As evaluated by the trial investigator
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.
Source: Wu et al, 2020;[17] ADAURA CSR.[71]

Table 16: 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	156 (46)	8 (2)	68 (20)	1 (<1)
Paronychia	85 (25)	3 (1)	5 (1)	0
Dry skin	79 (23)	1 (<1)	22 (6)	0
Pruritis	65 (19)	0	30 (9)	0
Cough	62 (18)	0	57 (17)	0
Stomatitis	59 (18)	6 (2)	14 (4)	0
Nasopharyngitis	47 (14)	0	35 (10)	0
Upper respiratory tract infection	45 (13)	2(1)	35 (10)	0
Decreased appetite	44 (13)	2 (1)	13 (4)	0
Mouth ulceration	39 (12)	0	8 (2)	0
Dermatitis acneiform	37 (11)	0	16 (5)	0

Abbreviation: AE, adverse event.
Source: Wu et al, 2020;[17] ADAURA CSR.[71]

B.2.10.2 *Safety overview*

Osimertinib as an adjuvant to complete resection showed an acceptable safety profile, with low rates of dose modification and treatment discontinuation, and no new safety concerns were reported.[17]

[redacted][71] The proportion of patients discontinuing or undergoing dose interruption due to adverse events was low (11% and 24%, respectively, with osimertinib, and 3% and 11%, respectively, with placebo).[17] Adverse events of special interest were ILD and cardiac events.[17] All ILD events occurred in the osimertinib arm, and all were mild or moderate in severity.[17] No meaningful difference in cardiac events was observed between treatment arms.[17] No new safety concerns with osimertinib were identified.[17] Thus, use of adjuvant osimertinib with or without chemotherapy results in significant improvements in clinical efficacy outcomes with a favourable safety profile.

B.2.11 *Ongoing studies*

The ADAURA trial is currently ongoing, with the final analysis anticipated for [redacted]. The final analysis will include statistical analysis of OS, to be conducted when ~94 deaths have occurred (~20% maturity) in the stage II–IIIA population.[17] An exploratory analysis of DFS will also be reported at this time.

No ongoing studies of osimertinib are relevant to this indication.

B.2.12 *Innovation*

Despite the curative potential for patients with completely resectable stage IB–IIIA NSCLC, many patients experience disease recurrence and a large proportion die within five years of surgery (post-resection mortality rates are 38–70% in patients with stage IB–III disease over approximately 5 years).[4] Current standard of care after complete resection is limited to adjuvant chemotherapy as an option for some patients, or active monitoring for those who are ineligible or choose not to have chemotherapy.[3] Although adjuvant chemotherapy is used with the aim of preventing recurrence and improving survival, it offers only a 5% absolute benefit in 5-year OS rates vs no chemotherapy.[4] In the absence of therapies providing better outcomes, there has been no meaningful innovation in the postoperative adjuvant setting for 20 years.[10]

Osimertinib, a third-generation EGFR-TKI, is the first targeted adjuvant therapy for EGFRm NSCLC and a new treatment in a stagnating adjuvant landscape, and therefore represents a step change in the treatment pathway for resectable disease. Osimertinib is a highly-selective therapy, capable of passing the blood-brain barrier.[42] The FLAURA trial of osimertinib in locally-advanced and metastatic EGFRm-positive NSCLC demonstrated significant improvements in PFS and OS with osimertinib vs standard of care (SoC) EGFR-TKIs, irrespective of the presence of CNS metastases.[68, 69] In addition, osimertinib has been recommended by NICE in the metastatic setting,[60, 64] and UK clinicians assert that osimertinib is the standard of care for metastatic disease.[18]

The Phase III, multinational, randomised controlled ADAURA trial is investigating the efficacy and safety of osimertinib (with or without chemotherapy) in patients with completely-resected stage IB–IIIA EGFRm-positive NSCLC. After ADAURA demonstrated overwhelming DFS benefits of osimertinib, the IDMC recommended the unblinding of ADAURA 2 years early.[1] The interim analysis showed that the risk of disease recurrence or death was significantly reduced by 80% vs placebo in the overall population (HR: 0.20; p<0.001) and significantly 83% reduced vs placebo in patients with stage II–IIIA disease (HR: 0.17; p<0.001).[17] Additionally, a clinically meaningful decrease in CNS recurrence or death was observed with osimertinib, and a reduction in distant metastases vs placebo.[17] These findings highlight the clinical potential of osimertinib for improving post-surgical outcomes including OS. The low proportion of patients experiencing CNS recurrence with osimertinib contrasts with trials of earlier-generation EGFR-TKIs, gefitinib and erlotinib, in the adjuvant setting, in which brain metastases drove disease recurrence.[11, 12] Brain metastases are the most common type of recurrence in NSCLC, impose a heavy burden, and mark a transition to incurable disease.[3, 5-8] Thus, by preventing brain recurrences in the resectable EGFRm population, osimertinib also meets a substantial unmet need.

Due to the unprecedented results from the ADAURA study, in July 2020, osimertinib was granted Breakthrough Therapy Designation in the USA for the adjuvant treatment of patients with stage IB–IIIA EGFRm NSCLC after complete tumour resection with curative intent. Because osimertinib is recognised as an innovative therapy for adjuvant treatment in patients with completely resected NSCLC, the ADAURA indication has been reviewed as part of Project Orbis. Project Orbis is an FDA OCE initiative with a focus on high-impact cancer drugs; providing a framework for concurrent submission and review of

oncology products among international partners. In 2020, the MHRA participated as part of Project Orbis as an observer and became a full participant as of 1st January 2021, however, each country remains fully independent on their final regulatory decision.

[redacted]

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

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

B.2.13.1.1 Summary of efficacy evidence

ADAURA

At the interim data cut of the Phase III ADAURA trial, osimertinib demonstrated an unprecedented, significant and clinically meaningful 80% reduction in the risk of disease recurrence or death vs placebo in patients with stage IB–IIIA NSCLC (HR: 0.20; p<0.001), a finding supported by [redacted] subgroup analyses (including disease stage and adjuvant chemotherapy use).[17, 71] For the subpopulation of patients with stage II–IIIA disease (those at highest risk of recurrence of the trial population), a risk reduction of 83% was observed vs placebo (HR: 0.17; p<0.001).[17]

Longer DFS with osimertinib vs placebo was generally driven by fewer recurrence events but, notably, treatment resulted in a lower proportion of distant metastases than locoregional recurrences.[17] By contrast, in the placebo group, the proportion of distant metastases was higher than locoregional recurrences. Therefore, if a patient does experience recurrence when treated with osimertinib, the patient is more likely to experience locoregional recurrence (compared to patients treated with SoC), and treatment options at this stage of the pathway include an additional chance at curative treatment (chemoradiation or surgery). Risk of CNS recurrence or death was significantly reduced by 82% with osimertinib in the overall population (HR: 0.18; p<0.0001).[17, 72]

[redacted][71] OS data were immature at the time of the interim data cut, although a numerical trend favouring osimertinib was observed.[17, 71]

[redacted][71]

Supporting study: FLAURA

Overall survival benefit has been demonstrated with osimertinib in the later-line Phase III FLAURA trial vs SoC EGFR-TKIs in an unresectable population (patients with untreated, advanced/metastatic NSCLC not amenable to surgery/radiotherapy; please see Appendix L.1 for a summary of this study).

At the second data cut of FLAURA (planned final OS analysis), OS was improved with osimertinib, with a significant 20% risk reduction vs SoC TKIs (HR: 0.80; p=0.046). This improvement was observed irrespective of presence of CNS metastases at baseline according to subgroup analyses.[68] In FLAURA, osimertinib demonstrated a 54% significantly lower risk of disease progression or death vs SoC TKIs (HR: 0.46; p<0.001). Median PFS was 19 months with osimertinib vs 10 months with SoC TKIs. The PFS benefit extended to patients with known CNS metastases at baseline, who experienced a significant 52% reduction in risk of progression or death vs SoC TKIs (HR: 0.48; p=0.014).[68] The duration of response was prolonged compared with other EGFR-TKIs, lasting for 18 and 10 months in the osimertinib and SoC TKI arms, respectively, in patients without CNS metastases; in patients with baseline CNS metastases, the duration of response was 14 and 8 months, respectively.[69]

B.2.13.1.2 Summary of safety evidence

Osimertinib was well-tolerated in ADAURA, with no new or unexpected safety concerns identified;[17] safety findings were largely in line with those previously observed in the FLAURA trial (see Appendix L.1.4). The proportions of patients discontinuing or undergoing dose interruption due to AEs were low in ADAURA (11% and 24%, respectively, with osimertinib, and 3% and 11%, respectively, with placebo).[17] [redacted][71] Common AEs with osimertinib in ADAURA included diarrhoea, paronychia, dry skin, pruritis, and stomatitis. Cardiac events and ILD were AEs of special interest; no meaningful difference in cardiac events was observed between treatment arms (5% in the osimertinib arm and 3% in the placebo arm), and ILD events (all of which were reported in the osimertinib arm) were all of mild or moderate severity.[17]

Safety findings in ADAURA are supported by additional evidence on osimertinib in previous clinical trials and real-world studies.[79, 80]

B.2.13.1.3 Discussion and conclusions

There is a substantial unmet need for treatments that reduce progression and improve survival after complete resection of NSCLC, when recurrence and mortality rates are high.[4] The findings of ADAURA show a significant and unprecedented DFS benefit with osimertinib compared with current clinical management, a finding that is clinically significant in this patient population.[17] The Kaplan-Meier curve for DFS with osimertinib in both the overall and stage II–IIIA populations separated from the placebo arm at approximately 12 weeks, and remained separated throughout the trial.[17] This suggests a sustained effect of osimertinib on recurrence. In addition, the effect on recurrence is expected to be maintained by the 3-year dosing period of the trial, which takes patients beyond the period of high recurrence risk and is in line with UK clinical expert opinion (Section B.2.13.2.2). The risk of CNS recurrence or death was also significantly lower with osimertinib than placebo, a finding that is anticipated to benefit patients by reducing the heavy HRQoL burden of brain metastases, and to impact OS due to the severity of metastatic vs locoregional disease.[6, 7, 28]

The findings from ADAURA are reinforced by the findings of FLAURA, despite the differences between these trials. Osimertinib demonstrated CNS activity in both trials, with an impact on CNS DFS in ADAURA and improved PFS vs SoC TKIs in patients with baseline CNS metastases in FLAURA; this CNS metastases benefit is expected to translate into OS benefit in ADAURA as seen in the FLAURA trial. The CNS findings vs the SoC TKI comparator arm in FLAURA highlight the key advantage of osimertinib vs other EGFR-TKIs, and explain why osimertinib demonstrates efficacy in the adjuvant setting, where two previous-generation TKIs (gefitinib and erlotinib) failed to meet a need for meaningful improvements in brain recurrence (Sections B.2.12 and B.2.13).[11, 12]

In conclusion, osimertinib demonstrates overwhelming efficacy as an adjuvant treatment option to complete resection with or without chemotherapy, significantly improving clinical outcomes vs placebo, which represents standard of care in the absence of novel adjuvant therapies. Given the high recurrence and brain metastasis rates in this patient group, osimertinib meets the substantial need for a targeted, high efficacy, well-tolerated treatment that crosses the blood-brain barrier to prevent CNS metastases.

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 an ongoing randomised, placebo-controlled, double-blinded, multicentre trial with balanced treatment arms, and is therefore robustly designed to assess safety and efficacy of osimertinib. The proportion of enrolled patients by disease stage who received adjuvant chemotherapy was higher than published rates of adjuvant chemotherapy in the UK (for patients diagnosed 2009–2011).[8] However, the rates of adjuvant chemotherapy use were considered reflective of clinical practice in England by clinicians consulted during an advisory board.[9] DFS benefits are observed irrespective of adjuvant chemotherapy use, suggesting an independent treatment effect with osimertinib.[17] The DFS benefit is also consistent across all subgroups including stage IB disease.[17] Patients in the osimertinib arm had fewer locoregional and distant recurrences than with placebo. However, when recurrence did occur, this was more frequently at locoregional sites in the osimertinib group, and by contrast, more frequently distant metastases in the placebo group.[17] A post hoc analysis of CNS recurrence found fewer CNS events in the osimertinib arm than the placebo arm.[17] Discontinuation and dose modification rates were low in the osimertinib arm, with no new safety concerns identified.[17] The majority of AEs reported were non-serious, of mild or moderate severity.[71]

Use of a placebo control in ADAURA is relevant to UK clinical practice, representing standard clinical management after resection, where patients may or may not receive adjuvant chemotherapy depending on eligibility (e.g. good performance status, and 1−2 involved lymph nodes) and patient choice, and are placed under active monitoring for disease recurrence.[3]

Treatment with osimertinib resulted in significant and clinically meaningful improvements in DFS vs placebo in the ADAURA study.[17] The primary endpoint of DFS is relevant to the clinical need in patients who have undergone complete resection because post-surgical recurrence is frequent in this population.[4] The clinical relevance of DFS was

confirmed by interviewed UK clinicians.[18] In patients with early-stage or locally-advanced (stage IB–IIIA) EGFRm NSCLC there is a particular need to prevent distant recurrence including CNS metastases, for which EGFRm is a risk factor.[5] Brain metastases are associated with poor HRQoL, increased economic burden, and very poor survival.[6, 7, 28] Therefore, improved DFS vs best clinical practice represents potential for a substantially reduced burden on patients and the healthcare system.

UK clinicians consulted through an advisory board suggested that a 3-year delay to progression would be a clinically significant advance and valuable for patients, particularly those with stage IIIA disease.[9] As well as extending patients' disease-free life, this maintains treatment beyond the 18–24 month period after resection when most relapses are expected to occur. Therefore, the DFS benefit observed with osimertinib is expected to translate into long-term survival benefits.[18] Clinicians state a number of reasons for this expectation, including: the unprecedented DFS benefit observed with osimertinib, unlike earlier generation EGFR-TKIs trialled in the adjuvant setting; the reduced risk of recurrence or death and the reduced rate of recurrence of distant/CNS metastases observed with osimertinib vs placebo; and the benefits in OS and CNS recurrence with osimertinib vs first- and second-generation EGFR-TKIs in the metastatic NSCLC setting (for example, significantly greater PFS and significantly greater OS with osimertinib vs SoC EGFR-TKIs, and consistent PFS benefit irrespective of baseline CNS metastases, in FLAURA).[18, 68] In addition, clinicians advised that the majority of patients experience disease recurrence within 2 years after surgery, and therefore felt that the 3-year treatment duration further reduces the risk of recurrence in the future. It is also worth noting that, at 5 years, clinicians advised that they generally discharge patients from their care and they would expect patients to no longer have an increased mortality risk compared with the age- and sex-matched general population. Therefore, a treatment duration of 3 years supports patients in remaining in a disease-free state, moving them towards this 5-year potential cure point.

Osimertinib is currently recommended for use in locally advanced or metastatic disease, including after treatment with other EGFR-TKIs where EGFR T790M mutations exist, and in untreated patients with EGFRm, but is not currently available to patients with early-stage disease.[60, 64] Addition to the treatment pathway as adjuvant therapy would make osimertinib the first targeted therapy for patients with resectable stage IB–IIIA EGFRm NSCLC. Provided in addition to current standard of care, osimertinib is expected to result in clinically meaningful and statistically significant improvements in DFS, and in longer-term outcomes such as OS.

B.2.13.2.2 Potential limitations

In the current ADAURA analysis, the key limitation is the immaturity of OS data,[17] as expected for this early interim cut. This is in line with the expectation that most patients will not yet have experienced a recurrence that will lead to death: interviewed clinicians stated that most relapses occur at 18–24 months, however the median duration of exposure in the ADAURA placebo arm was only 19 months.[18] Although osimertinib provides a significant OS benefit in FLAURA vs SoC TKIs (HR: 0.80; p=0.046), the impact of osimertinib on OS in resectable patients is currently not demonstrated.[68] Another limitation is the immaturity of DFS data, resulting from the IDMC

recommendation of early unblinding due to overwhelming efficacy. The majority of patients had not completed their 3-year treatment at the interim analysis [redacted][17, 71]

B.2.13.2.3 Discussion

Despite the immaturity of the ADAURA OS data, an OS benefit is expected. In ADAURA, patients were randomised to a 3-year treatment duration to maximise the benefits of surgery; this is crucial because recurrence often occurs soon after treatment.[17] Previous trials of first-generation EGFR-TKIs suggest a need for prolonged treatment duration. The Phase III RADIANT trial of erlotinib treated a population of completely resected stage IB–IIIA patients both with and without EGFRm-positive disease; in total, 161 EGFRm-positive patients (102 in the erlotinib arm and 59 in the placebo arm) were randomised to 2-year treatment.[12] The Phase III ADJUVANT trial of gefitinib enrolled 222 patients with completely-resected stage II–IIIA EGFRm-positive NSCLC, with a 2-year treatment duration of gefitinib (the comparator was vinorelbine plus cisplatin).[15] In the ADJUVANT and RADIANT trials, a narrowing of the DFS gap against the comparator arm at 36–48 months was observed for EGFRm-positive patients treated with gefitinib or erlotinib, suggesting a need for longer treatment, although small sample size was also detrimental.[48, 49] Moreover, offering patients adjuvant chemotherapy in addition to an EGFR-TKI may improve cure rates through combined modes of action.[13] The 3-year dosing of ADAURA is intended to treat patients beyond the 18–24 months at which recurrences commonly occur,[18] intended to increase survival. It is not yet known whether recurrences will be delayed only until treatment discontinuation. Interviewed UK clinicians suggested that a 6-year observation period should determine whether delayed recurrence has occurred, but stated that nonetheless, they would expect the DFS response to remain after 3 years.[18]

Previous trials of first-generation EGFR-TKIs in the adjuvant setting failed to demonstrate favourable OS;[12, 15, 81] however, a lack of DFS/OS correlation should not be assumed for osimertinib based on these findings. Unlike gefitinib and erlotinib, the mode of action of osimertinib includes penetration of the blood-brain barrier.[11, 13, 42] Thus, whereas DFS is driven by reduced extracranial recurrence with gefitinib, it is driven by reduced CNS recurrence with osimertinib.[11, 17, 71] A CNS benefit is expected to provide an OS benefit because of the severity of CNS recurrence.[82] Moreover, locoregional recurrences can be treated with chemoradiation, considered by UK clinicians to be a potentially curative option;[18] as a result, changing the ratio of recurrence types to increase the locoregional proportion is anticipated to increase the proportion of patients who are cured.

Clinicians stated in interviews that they would expect a significant DFS benefit to translate to an OS benefit, and ADAURA is ongoing to collect further survival data.[18]

B.2.13.3 *End-of-life criteria*

Osimertinib as an adjuvant to complete surgical resection in patients with stage IB–IIIA EGFRm NSCLC is not eligible as an end-of-life therapy: median OS in the placebo arm of the ADAURA trial was 48.2 months.

B.3. Cost effectiveness

- **A cost-effectiveness analysis from the NHS perspective was performed comparing osimertinib to placebo (active monitoring; with or without adjuvant chemotherapy) representing established clinical management for the adjuvant treatment of stage IB–IIIA EGFRm-positive NSCLC after complete tumour resection**
- **In the base case analysis, an ICER of £12,849 per QALY was produced for osimertinib versus placebo (active monitoring), with incremental total costs of [redacted] and QALYs of [redacted]. This cost-effectiveness result is well below NICE's standard WTP threshold range of £20,000–£30,000 per QALY**
    - 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. For the ADAURA indication, a PAS price of [redacted]
- **The mean ICER resulting from the probabilistic analyses was comparable to the deterministic base case results, indicating the model was robust with respect to parameter uncertainty. At a WTP threshold of £20,000 per QALY, the probability of osimertinib being cost-effective versus placebo (active monitoring) is 100%**
- **Deterministic sensitivity analyses indicated that the most influential parameters are the drug acquisition costs in the disease free and locoregional health states, resulting in a range of ICERs between £7,220 and £18,478 per QALY**
- **Scenario analyses that resulted in the lowest and highest ICERs are:**
    - When the discount rate for both costs and outcomes was reduced to 1.5%, the ICER decreased by 29% to £9,147 per QALY
    - When the health state utilities were replaced with data from published literature,[29] the ICER increased to £14,713 per QALY
- **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).[1] 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**
- **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-positive NSCLC after complete resection, when compared with established clinical management.**

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 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 health technology assessment (HTA) appraisals, and conference proceedings were performed to identify data not captured in the database searches.

Full details of the search are provided in Appendix G. However, no 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.

B.3.1.2 *Description of identified studies*

No relevant studies were identified for inclusion.

B.3.1.3 *Quality assessment of identified studies*

No relevant studies were identified for inclusion.

B.3.2 *Economic analysis*

As the SLR did not identify an existing economic evaluation of adjuvant therapy in completely resected, stage IB–IIIA EGFRm-positive NSCLC (with or without adjuvant chemotherapy), a *de novo* economic model was built in Microsoft Excel® to address the decision problem. The key characteristics of the model are outlined in Table 17.

Table 17: Characteristics of *de novo* economic model

Aspect	Details	Justification
Model structure	A 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 and TA632), 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

Aspect	Details	Justification
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)
Cycle length	4 weeks (28 days)	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	Due to limited post-recurrence follow-up data available from ADAURA at the data cut-off (January 2020), data from the CancerLinQ database was used
Clinical effectiveness – distant metastases	FLAURA trial	Due to limited follow-up data for distant metastasis from ADAURA at the data cut-off (January 2020), data from FLAURA is used as it is the key trial providing clinical data for osimertinib in the metastatic treatment setting of EGFRm NSCLC

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.

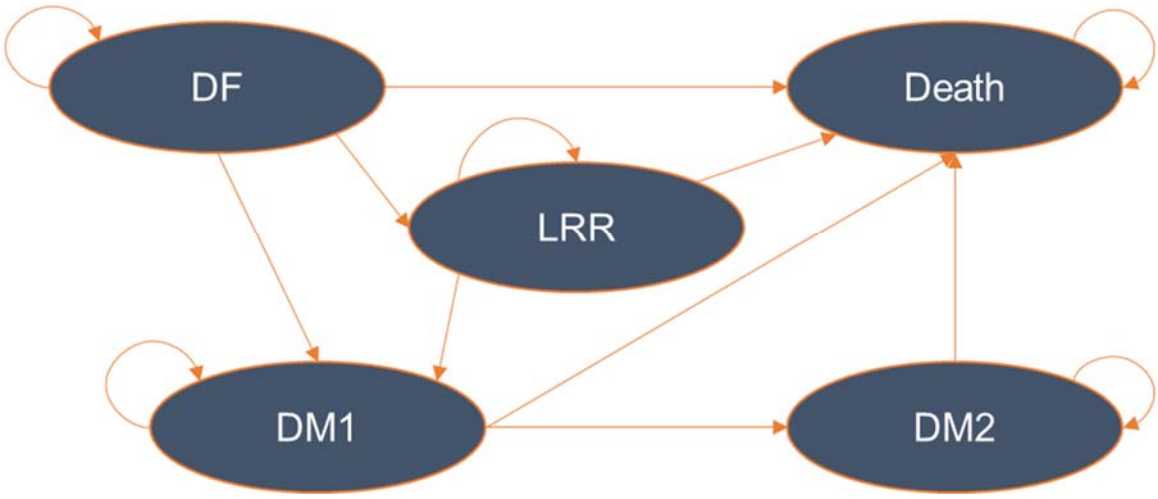
B.3.2.1 *Patient population*

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 9) and is therefore aligned with the anticipated label.

B.3.2.2 *Model structure*

A 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 13).

Figure 13: 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 weeks (28 days) to align with recurrent costs and timing of patients' treatment, and was 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; i.e. mean age from ADAURA) and gender distribution (70.1% female based on the overall population of ADAURA) 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), representing the maximum possible survival for any patient in this modelled population.

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.[83] 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.[83] 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% for both costs and outcomes.

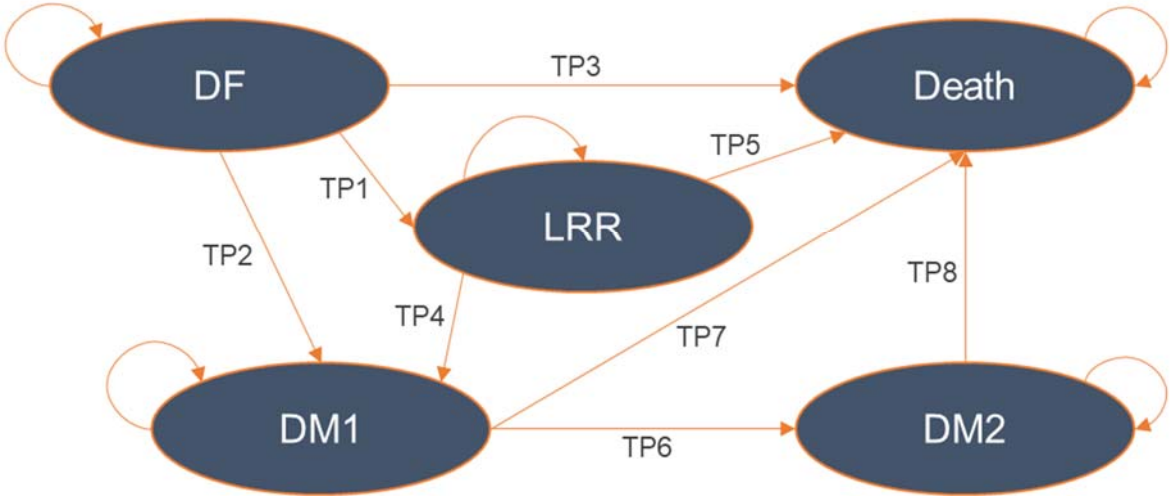
This type of model was considered appropriate for the decision problem, as both the structure and health states are in line with the clinical pathway outlined in Section B.1.3.4 (Figure 4), and are consistent with previous NICE technology appraisals in early-stage cancer (TA424,[84] TA569,[85] and TA632[86]) 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.[9]

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 14). 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 health state, or they can die. 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. Table 18 lists the data sources used for each transition.

1. **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.
2. **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.
3. **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 data cut-off (January 2020), so the probability of transitioning to this state is determined based on data from the CancerLinQ database.
4. **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 FLAURA trial data, which is the key trial of osimertinib versus SoC TKI (erlotinib/gefitinib) in the metastatic setting. This trial was used due to limited, immature overall survival data available from ADAURA.
5. **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 given the age and gender distribution of the cohort during the cycle period.[87]

Figure 14: 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 18: Overview of the data source used per transition

Transition	Data source
TP1: DF → LRR	ADAURA [71]
TP2: DF → DM1	ADAURA [71]
TP3: DF → DEATH	UK life tables [87]
TP4: LRR → DM1	CancerLinQ [88]
TP5: LRR → DEATH	UK life tables [87]
TP6: DM1 → DM2	FLAURA [89]
TP7: DM1 → DEATH	FLAURA [89]/ UK life tables [87]
TP8: DM2 → DEATH	FLAURA [89]

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

B.3.2.3 *Intervention technology and comparators*

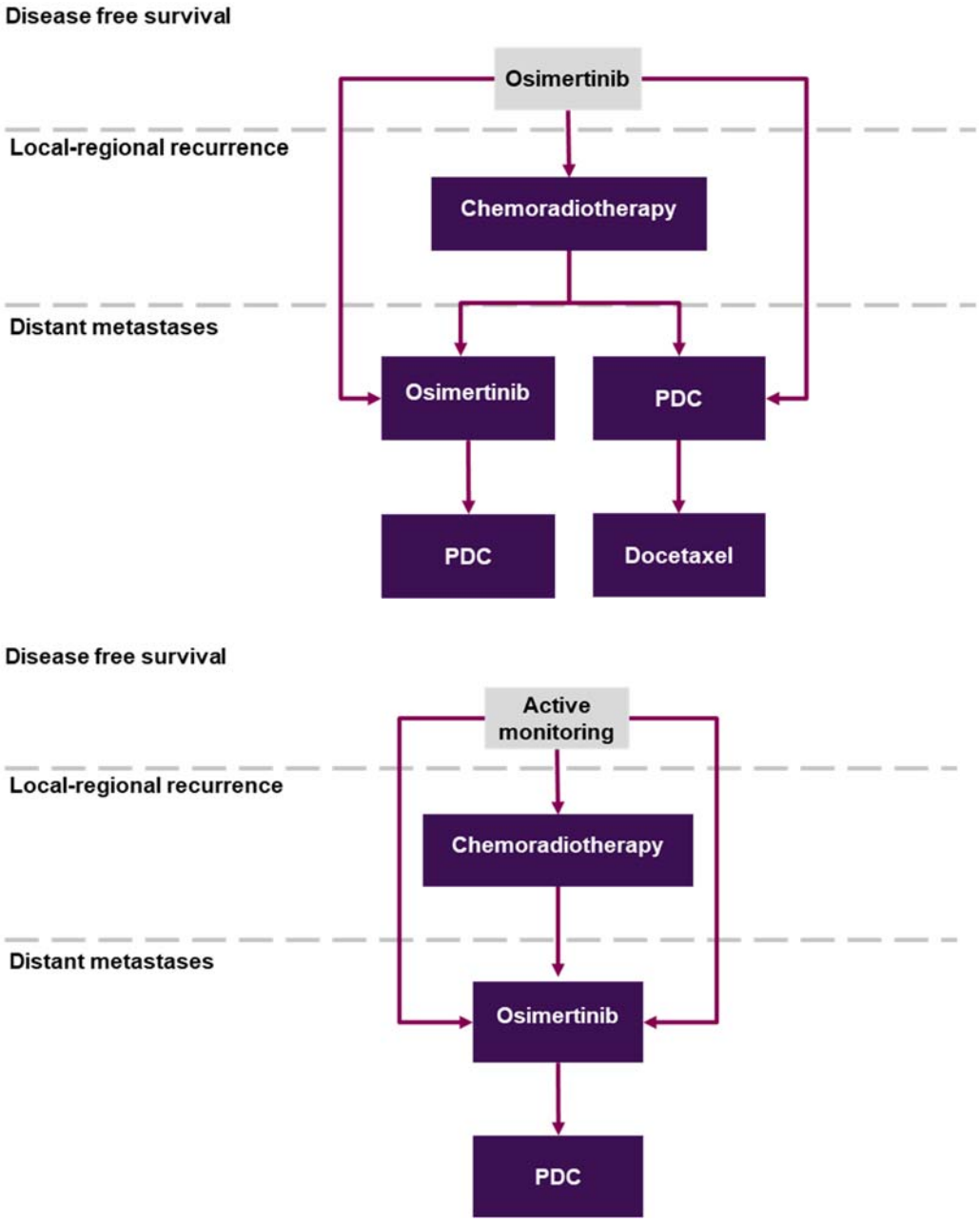
The ADAURA trial is the key data source of this cost-effectiveness analysis, in which osimertinib (intervention arm) is compared with placebo (comparator arm) in patients with completely resected, stage IB–IIIA EGFRm-positive NSCLC with or without adjuvant chemotherapy. The NICE decision problem states that the comparator for the current appraisal should be 'established clinical management without osimertinib' (which is, active monitoring).

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.

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 15 are considered in the model based on current and expected clinical practice suggested and validated by UK clinicians.[18] A detailed description of the treatment sequence is provided in Section B.3.5.2.1.

Figure 15: Treatment sequence applied in the model per osimertinib and placebo (active monitoring) treatment arms



Abbreviation: PDC, pemetrexed plus cisplatin.

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 17 and Table 18, 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).[71] As limited post-recurrence follow-up data were available from ADAURA at the data cut-off time-point (January 2020), parametric survival modelling was used to estimate the probability of transition from LRR to DM1 using data from CancerLinQ, a US real-world evidence database comprising over 1.4 million patients with a primary cancer diagnosis (Appendix L.2).[88] The transition probabilities from the distant metastases health states (DM1 and DM2) are primarily estimated from survival modelling applied to 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 L.1).[89] The FLAURA trial was the primary source of survival data used to inform the efficacy of treatment in the metastatic setting in TA654.[90]

Where data from relevant trials were not available to generate the transition probability of entering the death state, general population mortality was applied using UK National Life Tables 2017–2019.[87]

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 via a survey of six UK clinicians.[18] 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 six 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.[18] 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.3.3.6).

B.3.3.1.1 Parametric extrapolation methods

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 18. Several candidate distributions were fitted to the data and assessed for “goodness of fit” (based on the Akaike information criterion [AIC] and Bayesian Information Criterion [BIC]). 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) 14,[91] all standard parametric functions (exponential, Weibull, log-logistic, lognormal, generalised Gamma and Gompertz) were fitted to the patient-level data to select the most appropriate.

The NICE DSU TSD 14 states that the same parametric function should be used across both treatment arms where feasible[91], as this ensures consistency and limits potential problems such as curves crossing over one another. As such, this approach was implemented in the analysis. Flexible survival extrapolations covered by NICE DSU TSD 21[92] were not run as at the time of data cut-off (January 2020) DFS and OS data from ADAURA trial were not mature enough to run such models. Therefore, a state transition modelling approach was considered instead of more flexible methods.

As described by Williams et al, 2017,[93] 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. 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 (AIC) of individual transitions do not by definition correspond to assessing the state occupancy probabilities that are ultimately of interest.[93] Alongside visual inspection, the goodness-of-fit was also evaluated based on the mean squared error (MSE) of the predicted model versus the Kaplan-Meier. Therefore, the resultant model was selected based upon a visual inspection of the combined DFS and OS curves, that achieved a good fit to the observed KM data (evaluated by the MSE diagnostic test) and were deemed clinically plausible, as evaluated by an independent UK advisory board held in November 2020. To achieve a clinically realistic and good fit of the data to the combined DFS and OS curves, survival curves applied for individual transitions were assessed primarily visually (as recommended by Williams et al, 2017[93]) for clinical plausibility. However, where several curves were deemed viable in terms of clinical plausibility and visual fit to the data, statistical fit (using fit based on AIC/BIC values and MSE) was also taken into account for the purpose of curve selection.

B.3.3.1.2 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. This 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.[91] 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. The visual inspection of this plot is more important than the test; however, a p-value is also generated as the result of a test of non-negative slope.[94]

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.[93]

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 as long as 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 was not reached in the osimertinib arm compared to 27.5 months (95% CI: 22.0, 35.0) in the placebo (active monitoring) arm. At the time of data cut-off (January 2020), 19.5% of patients in the overall trial population had been followed for at least 3 years. The lack of completeness of these data, on top of the truncated follow-up period in ADAURA (based on advice from the IDMC to unblind the trial early due to overwhelming efficacy of osimertinib), meant that extrapolation techniques were essential to model DFS over a lifetime time horizon (37 years).

Parametric functions were applied to patient-level ADAURA data to facilitate extrapolation beyond the follow-up period, as per NICE DSU 14 guidance.[91] However, since the ADAURA study uses DFS and OS as endpoints, the datasets required for extrapolation of each transition probability cannot be derived directly. Therefore, the competing risks methodology described by Williams et al, 2017,[93] was used to generate each transition's dataset for use in the model. 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

As cure is a prospective important outcome of the patient population considered in this economic evaluation, a cure assumption was included to fully capture the expected functional cure of these patients beyond the currently available follow up DFS data from ADAURA. The rationale supporting this important component is outlined below.

Feedback from KOLs and clinical practice

Interviews conducted with six UK clinicians confirm that in UK clinical practice, patients with completely resected early-stage NSCLC are typically discharged from care after 5 years if they have not experienced disease recurrence. Patients are at greatest risk of recurrence 18–24 months post-surgery and therefore if patients remain disease free at 5 years they can be considered functionally cured. Clinicians generally consider the risk of recurrence to be very low after 5 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 5 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).[18]

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.[17, 71] 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).[18]

When considering the reduction in disease recurrence observed with osimertinib in ADAURA it is notable that, when recurrence did occur, this was more frequently at locoregional sites in the osimertinib group, and by contrast, more frequently distant metastases in the placebo (active monitoring) group.[17] Thus, if a patient does experience recurrence when treated with osimertinib, the patient is more likely to experience locoregional recurrence (compared with patients treated with SoC), and treatment options at this stage of the pathway include an additional chance at curative treatment (chemoradiation). The risk of CNS recurrence or death was also significantly reduced by 82% with osimertinib in the overall population (HR: 0.18; p<0.0001).[17, 72] Thus, the reduction in distant metastases is an important clinical benefit of osimertinib, that suggests improved survival and a potential for cure vs SoC.

Previous NICE appraisals

A search was conducted for NICE oncology appraisals that have previously used a cure assumption to develop economic models. In the adjuvant setting, two early breast cancer appraisals (TA569, TA632) and one melanoma appraisal (TA553) were identified that explicitly modelled cure.[85, 86, 95] Two non-adjuvant appraisals were identified in leukaemia (TA554 and TA450) that also explicitly modelled cure.[96, 97] 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.

Published literature

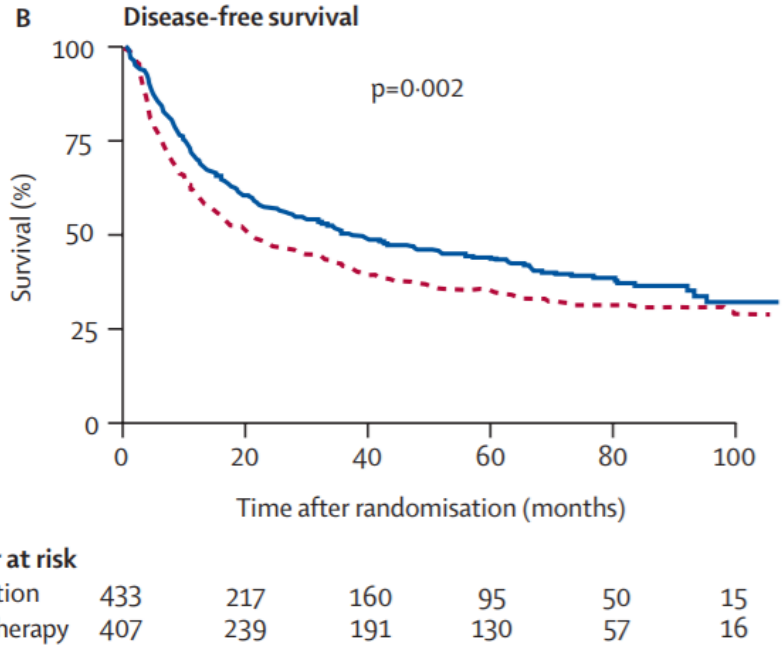
To further support the assumption of functional cure in the economic analysis, a targeted literature search was conducted to identify published studies evaluating long term DFS rates (> 3 – 4 years) in patients with early stage (stage I-III) NSCLC following complete surgical resection. Although published data on longer-term survival outcomes in this setting are limited – particularly in stage IB–IIIA EGFRm-positive NSCLC – several studies[4, 98, 99] 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.[4, 98, 99] 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 time period (up to 48 months) that, according to prior studies, appears to correspond with an elevated recurrence rate. However, this elevated recurrence rate is more pronounced in the placebo (active monitoring) arm than in the osimertinib arm at the time of data cut-off. As a result, 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 (Section B.3.3.7).[18]

One trial was identifed 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.[99] 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 O).

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 16), 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.

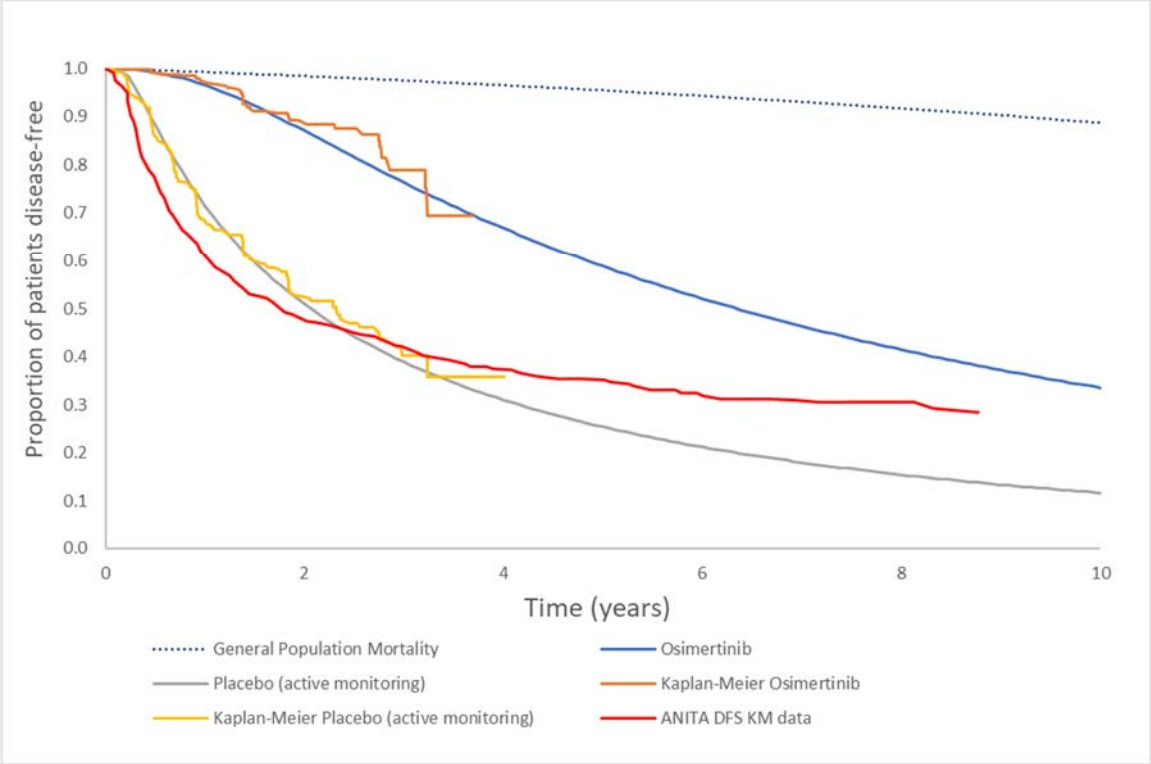
Figure 16: ANITA study DFS



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.[100] 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]: generalised gamma), see Section B.3.3.6) 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 17 below). Applying a 0% cure proportion in the ADAURA placebo (active monitoring) arm (patients are no longer at risk of recurrence and only subject to background mortality) suggests that the risk of disease recurrence beyond 48 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.

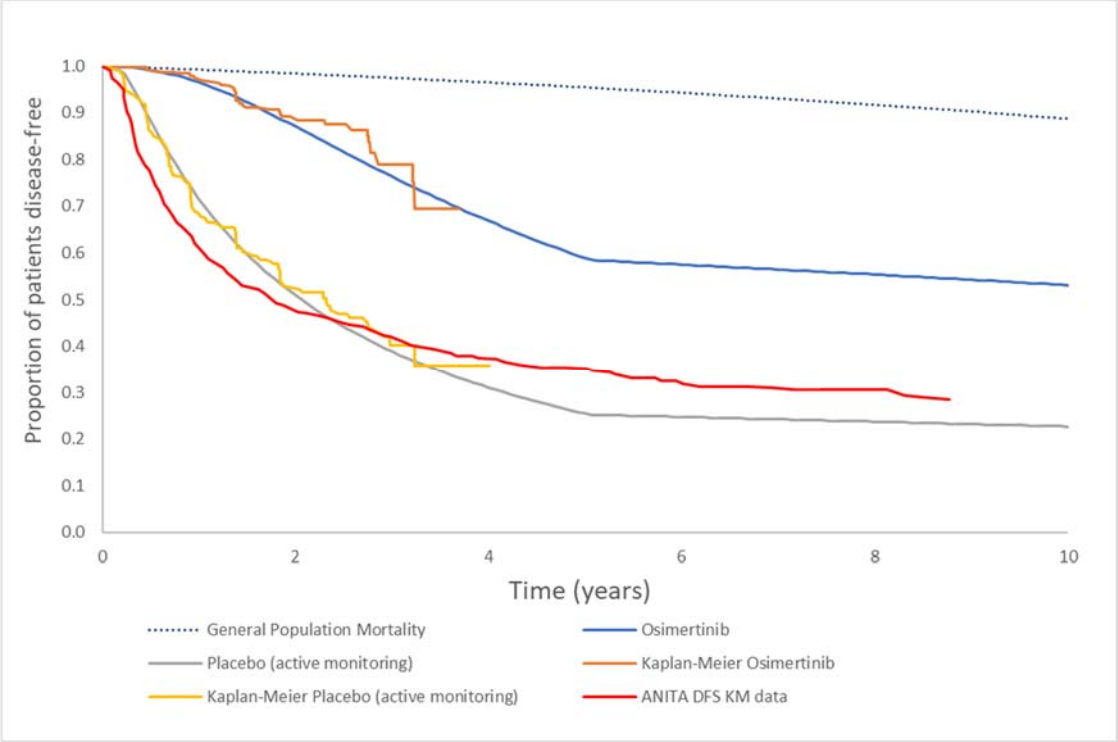
Figure 17: Unadjusted ADAURA DFS extrapolations versus ANITA DFS (0% cure proportion)



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

Conversely, when the assumption of a cure rate of 95% at 5 years was applied to both arms in the model, the predicted DFS rates from the ADAURA placebo (active monitoring) arm were more consistent with the longer term DFS KM curve from ANITA (see Figure 18).

Figure 18: 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 performed to estimate a plausible rate of cure in patients with stage IB–IIIA surgically-resected NSCLC. A series of parametric mixture cure models (MCM) 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.[101] Overall the MCM analysis estimated cure fraction rates ranging from 16–31% and predicted DFS rates at 5 years of 33–35% for the ANITA trial (see Table 19). The results of the analysis were consistent with opinion from the UK clinical expert panel, providing further support for the curative potential in this setting. 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 (combined DFS at 5 years: 25.6%; 95% assumed to be cured at 5 years: 24.3%) is comparable to the range estimated in this analysis (Table 19). This supports the validity of the model extrapolations, and the use of the landmark method to predict cure.

Table 19: Estimated cure fraction rates and DFS 5-year rates using mixture cure models applied to the ANITA trial

Model	AIC	Cure fraction (%)	DFS at 5 years (%)
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.

Summary and approach used in the model

In summary, as described above, a cure assumption was included in the economic analysis based on expert clinical opinion, ADAURA clinical data and supporting evidence from the published literature. Interviewed clinicians advised that, in UK clinical practice, patients who remain disease free at 5 years post-surgery can be considered to be cured, are discharged from care, and can be reasonably assumed to have a mortality risk similar to that of the general background population.[18] 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).[18] Indeed, as described in Section B.2, 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)).[17] Not including a cure assumption would have been clinically unrealistic given that, as agreed by the interviewed clinicians, the extrapolated ADAURA DFS curves are likely to overestimate the long-term rate of disease recurrence and are therefore overly pessimistic for an early-stage resected population[18]

To align with accepted methodology in previous NICE appraisals, in the base case analysis 95% of patients in the DF health state were assumed to be functionally cured after 5 years. Patients who were cured were deemed to no longer be at risk of disease recurrence, or at risk of dying from NSCLC; these patients were instead subject to age-matched general population mortality. At the 5-year time point health state costs for cured patients 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 of 5 years (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.

Nevertheless, despite the arguments outlined above, due to the immaturity of DFS data in the ADAURA trial, uncertainty around the cure assumption was tested in scenario analyses. Scenarios tested included applying different cure timepoints, varying the percentage of patients cured, and applying a more continuous flow in the percentage of patients cured by using an interim warm up period of 1 year before 5 years, when 95% of patients are assumed to be cured (rather than a sudden application of the cure assumption from 5 years).

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. Parametric curves were fitted to the data presented in Figure 19 applying the methods described below.

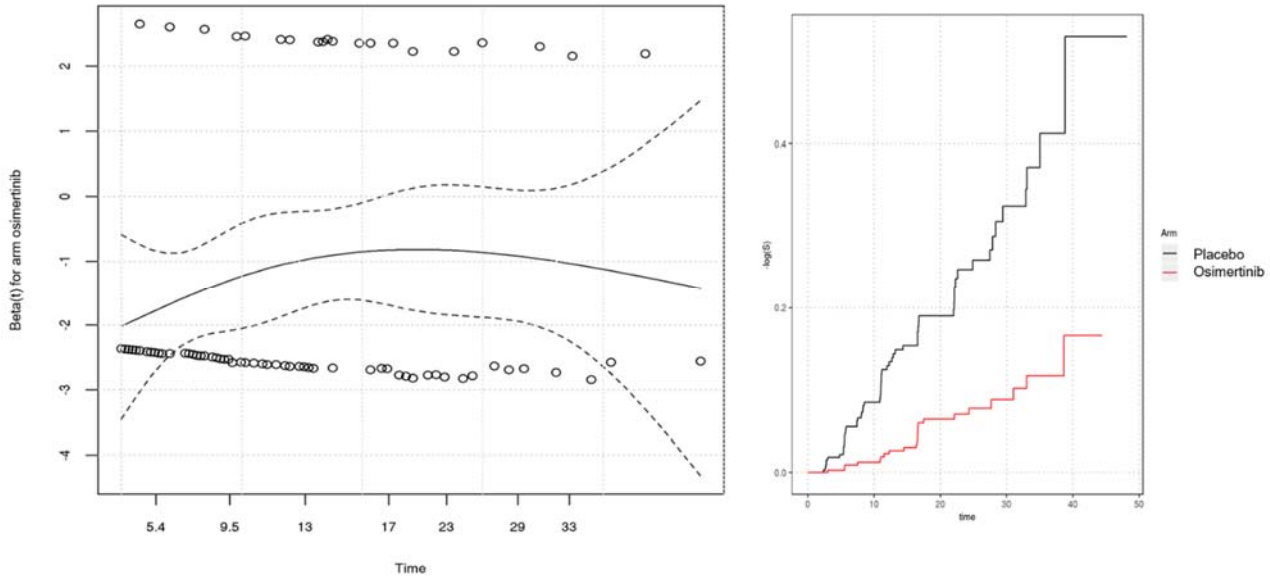
Figure 19: KM curves for time to locoregional recurrence in the osimertinib and placebo (active monitoring) arms of ADAURA

Abbreviation: KM, Kaplan-Meier.

Assessment of the proportional hazards assumption

In Figure 20 the cumulative hazards plot and the Schoenfeld residuals plot can be found for the transition DF to LRR with the statistical test results in Table 20. The Schoenfeld residuals plot and the Schoenfeld residuals test (p=0.286) indicate that the proportional hazards assumption holds, and as such both individual fits and combined fits (single dependent model with a treatment coefficient for osimertinib) can be used. However, since the proportional hazards assumption does not hold for all transitions (see TP2 in Section B.3.3.3.3 and TP8 in Section B.3.3.5.3), individual fits are applied to all transitions. Individual fits of the same parametric functions were applied to align with NICE DSU TSD 14 which recommends using the same parametric function for both treatment arms where feasible.[91]

Figure 20: Schoenfeld residuals and cumulative hazard plot for the transition DF to LRR (TP1)

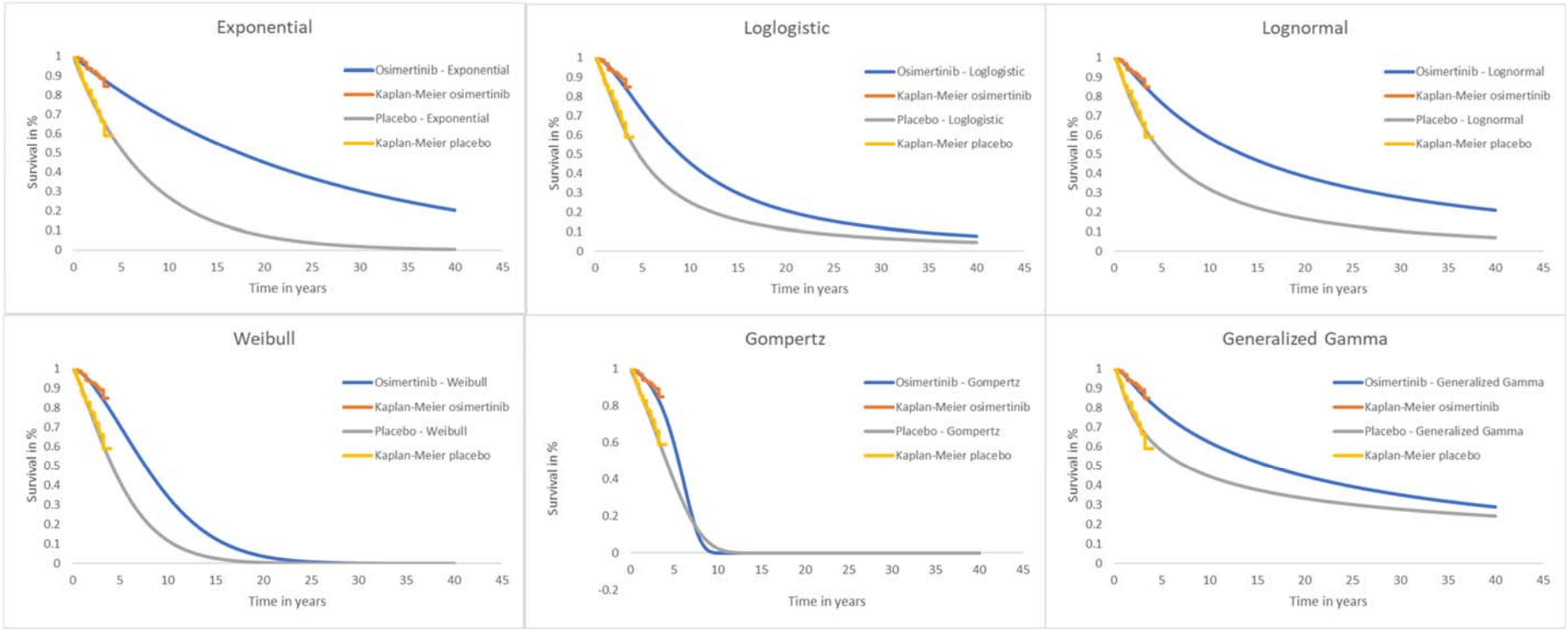


Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DF, disease-free; LRR, locoregional recurrence.

Goodness of fit for parametric distributions

Parametric distributions were assessed for their goodness of fit based upon visual inspection and whether the extrapolation was clinically realistic. Figure 21 shows the fits and extrapolations for the transition from DF to LRR (TP1), with the AIC and BIC values presented inTable 20. Based on visual inspection of the extrapolations and the expectation of six UK clinical experts that functional cure is expected both in the osimertinib and placebo (active monitoring) arm,[18] the exponential, Weibull, Gompertz and loglogistic distributions can be excluded as they produce pessimistic long-term survival estimates incompatible with the underlying functional cure assumption (as described in B.3.3.3.1). From the remaining distributions, the lognormal distribution fits the KM data best, both visually (i.e. maintaining the expected treatment effect between the arms) and statistically. Based on the functional cure expectations by clinicians, both of these distributions present a clinically more realistic scenario than the previously excluded distributions. As presented in Table 20, the lognormal curve results in the lowest AIC and BIC in both arms. Therefore, this distribution was selected for the base case analysis.

Figure 21: Extrapolations for DF to LRR (TP1)



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

Table 20: AIC and BIC values for the fitted distributions to the transition DF to LRR

		Osimertinib		Placebo (active monitoring)	
Model	**Clinically viable**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	No	314.32	318.15	685.82	689.66
Weibull	No	310.66	318.32	683.06	690.73
Loglogistic	No	310.55	318.20	681.99	689.67
LOGNORMAL	Yes	309.89	317.54	678.46	686.13
Gompertz	No	312.82	320.47	686.36	694.03
Generalised gamma	Yes	311.86	323.33	679.09	690.60

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.

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

KM data

For the transition from the DF to DM1 state, KM data for the time to distant metastases from the ADAURA trial was used. Parametric curves were fitted to the data presented in Figure 22 applying the methods described below.

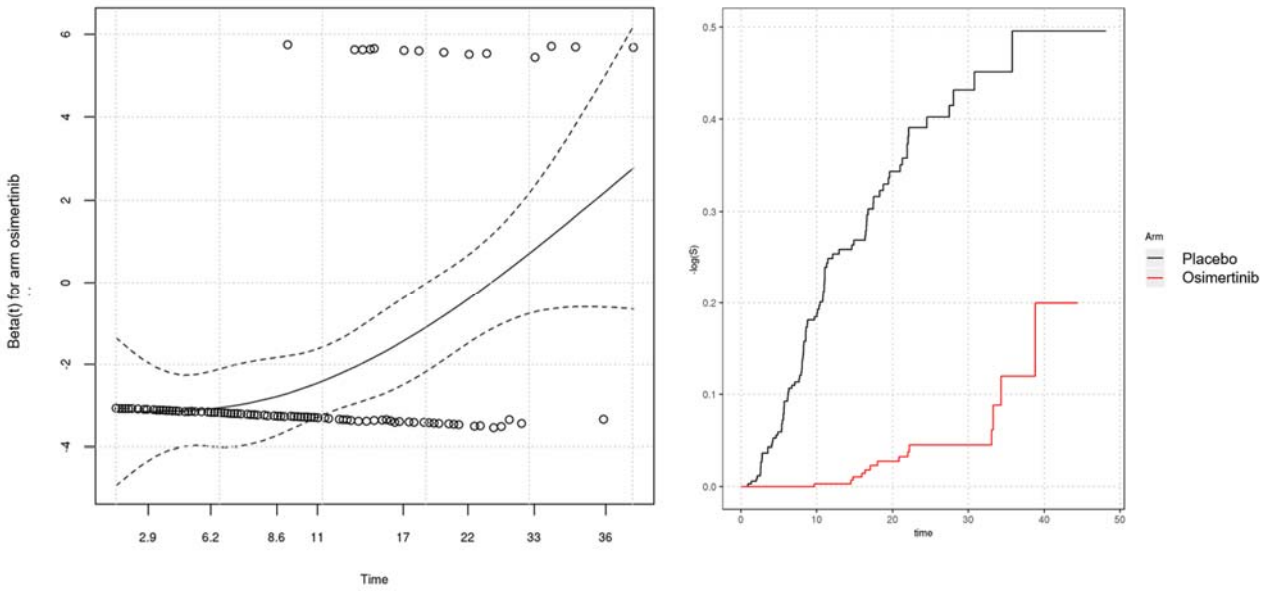
Figure 22: KM curves for time to distant metastases survival in the osimertinib and placebo (active monitoring) arms of ADAURA

Abbreviation: KM, Kaplan-Meier.

Assessment of the proportional hazards assumption

The Schoenfeld residuals plot and the cumulative hazard plot for the transition from DF to DM1 is shown in Figure 23, with the statistical test results in Table 21. Since the Schoenfeld residuals plot does not show a linear trend with a gradient of zero, the proportional hazards assumption does not hold ($p<0.001$) meaning combined fits of the same distribution are not a viable option and individual fits must be used. Therefore, individual fits of the same distribution were applied to align with NICE DSU TSD 14, which recommends using the same parametric function for both treatment arms where feasible.[91]

Figure 23: Schoenfeld residuals and cumulative hazard plot for the transition DF to DM1 (TP2)

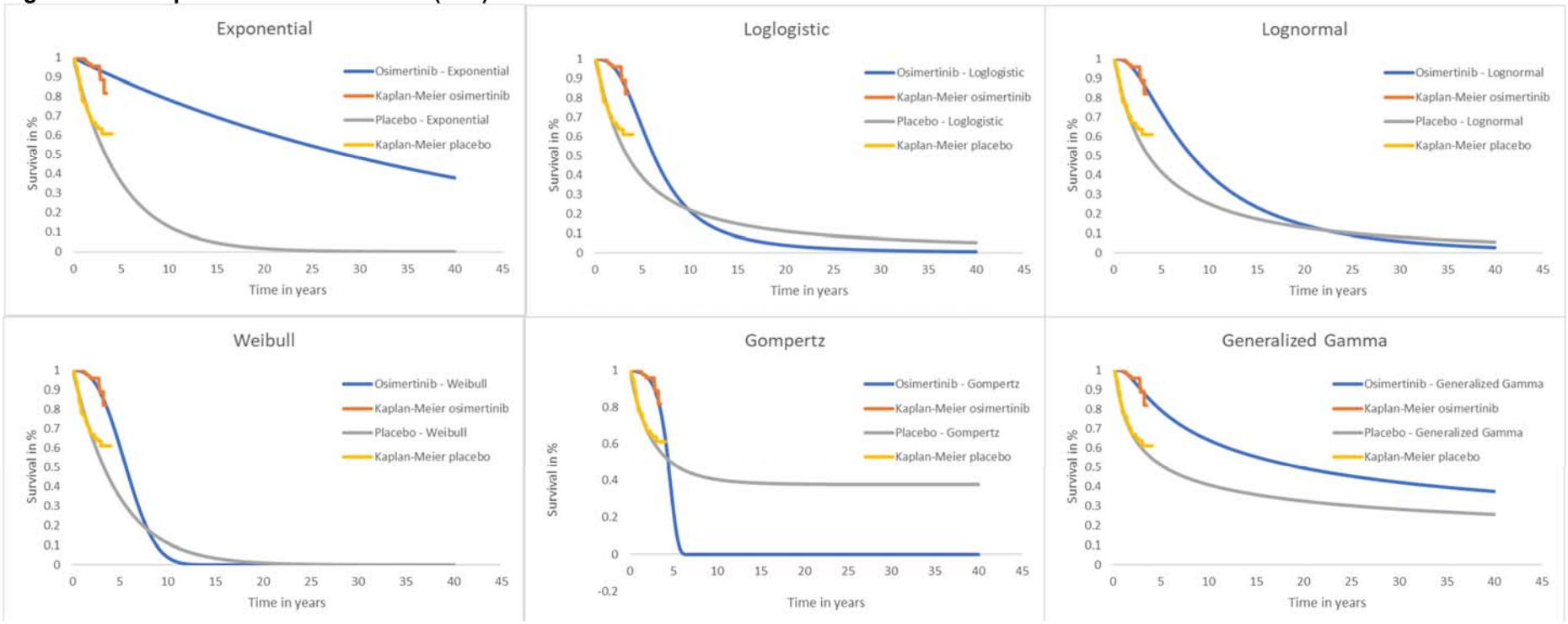


Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; TP2, transition probability 2.

Goodness of fit for parametric distributions

Parametric distributions were assessed for their goodness of fit based upon visual inspection and whether the extrapolation is clinically realistic. Figure 24 shows the fits and extrapolations for the transition from DF to DM1 (TP2), with the AIC and BIC values presented in Table 21. Based on visual inspection of the extrapolations and the expectation of six UK clinical experts that cure is expected both in the osimertinib and placebo (active monitoring) arm, the exponential, Weibull, Gompertz and loglogistic distributions can be excluded.[18] From the lognormal and generalised gamma distribution, the generalised gamma distribution provides a clinically more plausible estimate and also the best statistical fit (i.e. the lowest AIC and BIC values as shown in Table 21) in the placebo (active monitoring) arm. For the osimertinib KM data, the lognormal distribution provides the best statistical fit (Table 21), however, the curves cross each other, which is not considered clinically plausible; the generalised gamma curves were therefore considered more clinically plausible, and this distribution was selected for this specific transition for both arms. It also aligns with the recommendation in the NICE DSU 14 document that the same parametric functions should be used for the treatment arms where possible.[91]

Figure 24: Extrapolations for DF to DM1 (TP2)



Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; TP2, transition probability 2.

Table 21: AIC and BIC values for the fitted distributions to the transition DF to DM1 (Independent Models)

		Osimertinib		Placebo (active monitoring)	
Model	**Clinically viable**	**AIC**	**BIC**	**AIC**	**BIC**
GENERALISED GAMMA	Yes	195.16	206.64	974.42	985.93
Lognormal	No	193.49	201.14	979.52	987.20
Loglogistic	No	194.17	201.82	987.45	995.12
Gompertz	No	196.52	204.18	990.13	997.81
Exponential	No	206.01	209.84	991.11	994.95
Weibull	No	194.19	201.84	992.91	1000.58

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

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

At the ADAURA data cut-off (January 2020), very few deaths had occurred among stage IB–IIIA patients who remained DF (0 in the osimertinib arm and 2 in the placebo (active monitoring) arm).[17, 71] This data immaturity meant 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.[87]

B.3.3.4 *Modelling from locoregional recurrence (LRR) (TP4 and TP5)*

Due to limited post-recurrence follow-up data available from the ADAURA trial at the data cut-off (January 2020), the transitions from local/regional recurrence (LRR) to 1st line treatment of distant metastasis (DM1) was modelled using CancerLinQ data (Appendix L.2). This is a real-world database, collecting electronic health record (EHR) 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 ([redacted]).

[redacted].

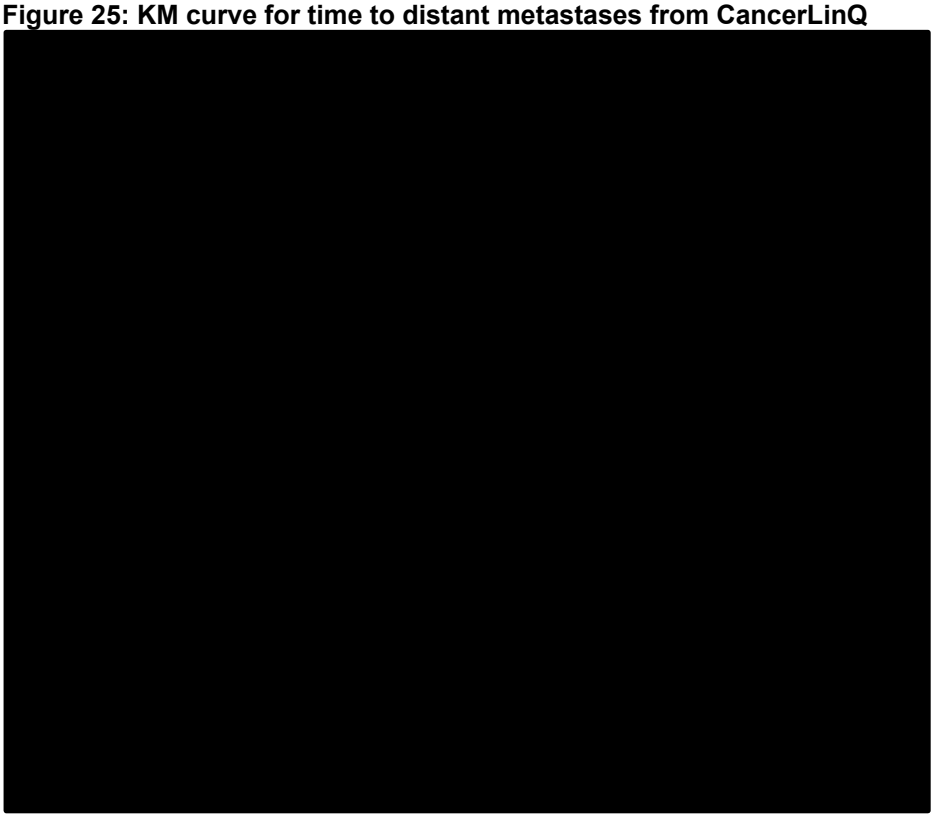
In the absence of available data from ADAURA at data cut-off, the transition probability from LRR to DM1 was assumed to be equivalent between the osimertinib and placebo (active monitoring) arms. The use of these data for the model was supported by UK clinical experts, who considered the patient population comparable with the ADAURA patient population and generalisable to UK practice (table with baseline characteristics of patients from CancerLinQ is presented in Appendix L.2.2).[18]

B.3.3.4.1 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 25 applying the methods described below.

Figure 25: KM curve for time to distant metastases from CancerLinQ



Abbreviation: KM, Kaplan-Meier.

Assessment of the proportional hazards assumption

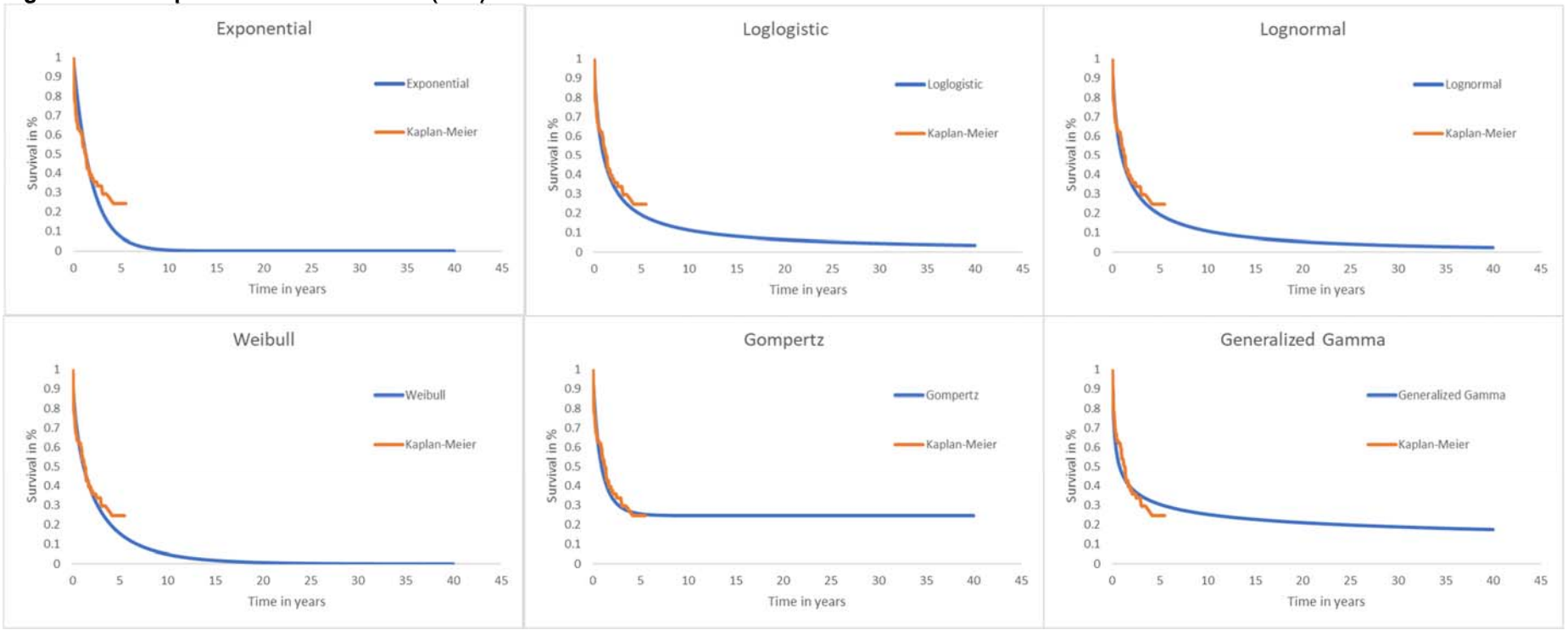
Since the data were analysed as one group, no proportional hazards assumption testing was required.

Goodness of fit for parametric distributions

Parametric distributions were assessed for their goodness of fit based on visual inspection and whether the long-term extrapolation is clinically plausible. Figure 26 shows the fits and extrapolations for the transition from LRR to DM1 (TP4), with the AIC and BIC values presented in Table 22.

Based on visual inspection of the extrapolations and clinical plausibility, the exponential and Weibull curves were excluded because of their pessimistic long-term survival estimates (providing a poor fit compared to the tail of the KM curve), external clinical data and expert opinion, while the Gompertz and generalised gamma distributions were excluded because of their optimistic long-term estimates, which are unrealistic for patients at this stage. The lognormal and loglogistic distributions appear similar based upon visual inspection, however AIC and BIC values indicate the lognormal distribution is preferred based on best statistical fit (Table 22).

Figure 26: Extrapolation of LRR to DM1 (TP4)



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

Table 22: 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.

B.3.3.4.2 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 unavailable other dataset for patients in the LRR state, this transition was modelled using background mortality from the age-adjusted UK population.[87] 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.3.3.5 *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, a completed Phase III, double-blind, randomised, controlled trial to assess the efficacy and safety of osimertinib versus gefitinib or erlotinib, as first-line treatment in patients with locally advanced or metastatic EGFRm-positive NSCLC (stage IIIB or IV) that is not amenable to curative surgery or radiotherapy (patient baseline characteristics are provided in Appendix L.1.2).[89] These data formed the basis of TA654 which assessed osimertinib as first line therapy for EGFRm-positive advanced NSCLC, and were considered clinically plausible for modelling distant metastases in the current model by six UK clinical experts.[18] 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,[93] 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 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 (bases on time to treatment discontinuation).

Following input from six UK clinical experts,[18] in the base case analysis it is assumed that retreatment with osimertinib in the DM1 state would be possible (Figure 15). However, the proportion of patients who would receive retreatment with osimertinib is unknown 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. 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 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.[18] However, in the base case retreatment with osimertinib is assumed to occur at 5 years. This time point was selected as feedback from interviews with clinicians also suggested patients in current clinical practice are most at risk of recurrence within 18–24 months post-surgery.[18] Therefore, the model applies this conservative assumption by adding the 18 to 24-month risk period to the end of the three-year treatment duration (i.e. 5 years from treatment initiation). The 5-year retreatment time point also aligns with the 5-year time point for cure creating alignment and internal consistency in the model. However, scenario analyses are also provided exploring the impact of retreatment at 4 and 6 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 5–year time point, and alternative proportions are also explored in scenario analyses.

For the remaining patients, it was assumed they would be treated with platinum doublet chemotherapy. However, as the standard of care in FLAURA is SoC TKI (erlotinib/gefitinib) the efficacy of chemotherapy might be overestimated in the model by applying transition probabilities reflective of a more efficacious therapy than chemotherapy in the DM state. The IPASS study[102] compared gefitinib versus carboplatin/paclitaxel in Asian patients with EGFR mutation-positive advanced NSCLC and showed that although the OS with gefitinib and carboplatin/paclitaxel is similar, gefitinib outperforms carboplatin/paclitaxel in terms of the PFS endpoint. A network meta-analysis based on this study estimated a PFS HR of 0.43 comparing chemotherapy to gefitinib.[103] An exploratory scenario analysis was thus conducted to test the impact of adjusting the efficacy of gefitinib versus chemotherapy by applying a HR of 0.43 to the transition from DM1 to DM2 (TP6). Additional evidence from a network meta analysis of studies of first-line TKIs in advanced EGFRm NSCLC indicated that the HR of PFS for first generation TKIs (erlotinib and gefitinib) was 0.36 to 0.43.[103]

Finally, it is assumed that all patients who received placebo (active monitoring) in DF will get treated with osimertinib at DM1. As osimertinib is the most potent and efficacious TKI compared to older TKIs also noted by clinicians, it is assumed that it would be a preferred treatment over other treatments for these patients.

B.3.3.5.1 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 27 applying the methods described below.

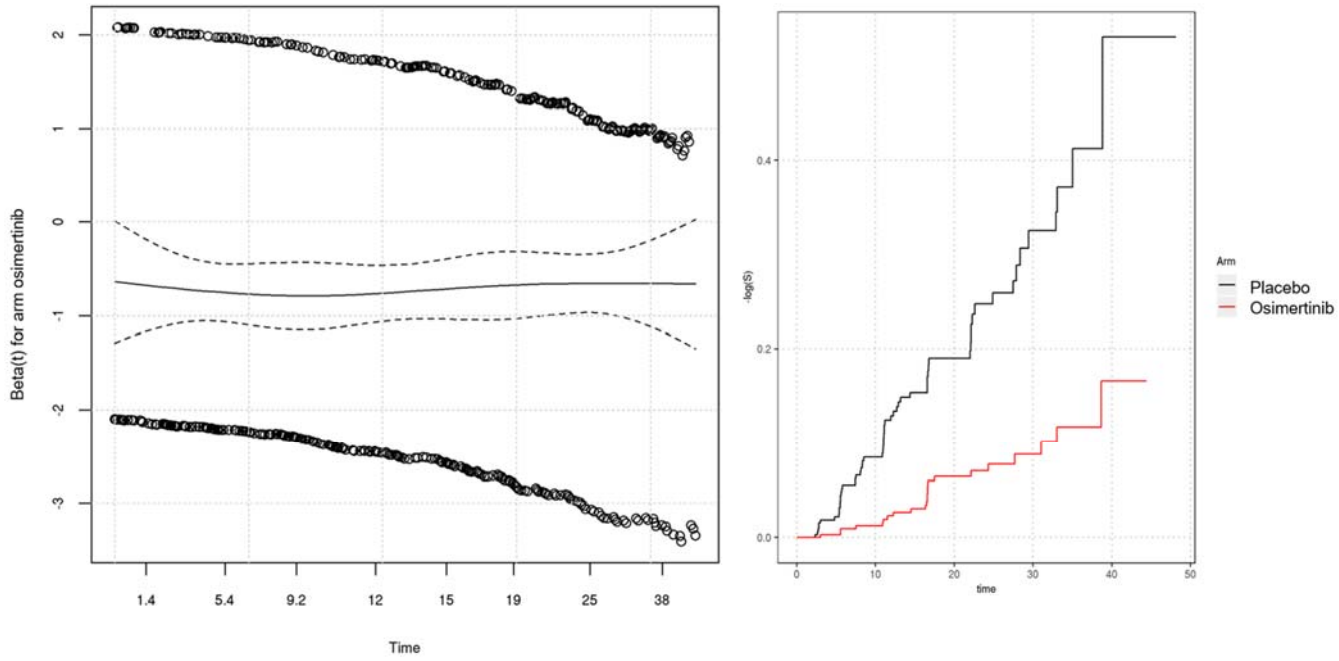
Figure 27: KM curves for the time to discontinuation of treatment (censoring deaths) in the osimertinib and placebo (active monitoring) arms of FLAURA

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 28, with the statistical test results provided in Table 23. 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. For consistency with the parametric modelling based on the ADAURA DCO1 DFS data, individual fitted models were applied for the base case analysis.

Figure 28: Schoenfeld residuals and cumulative hazard plot for the transition DM1 to DM2 (TP6)

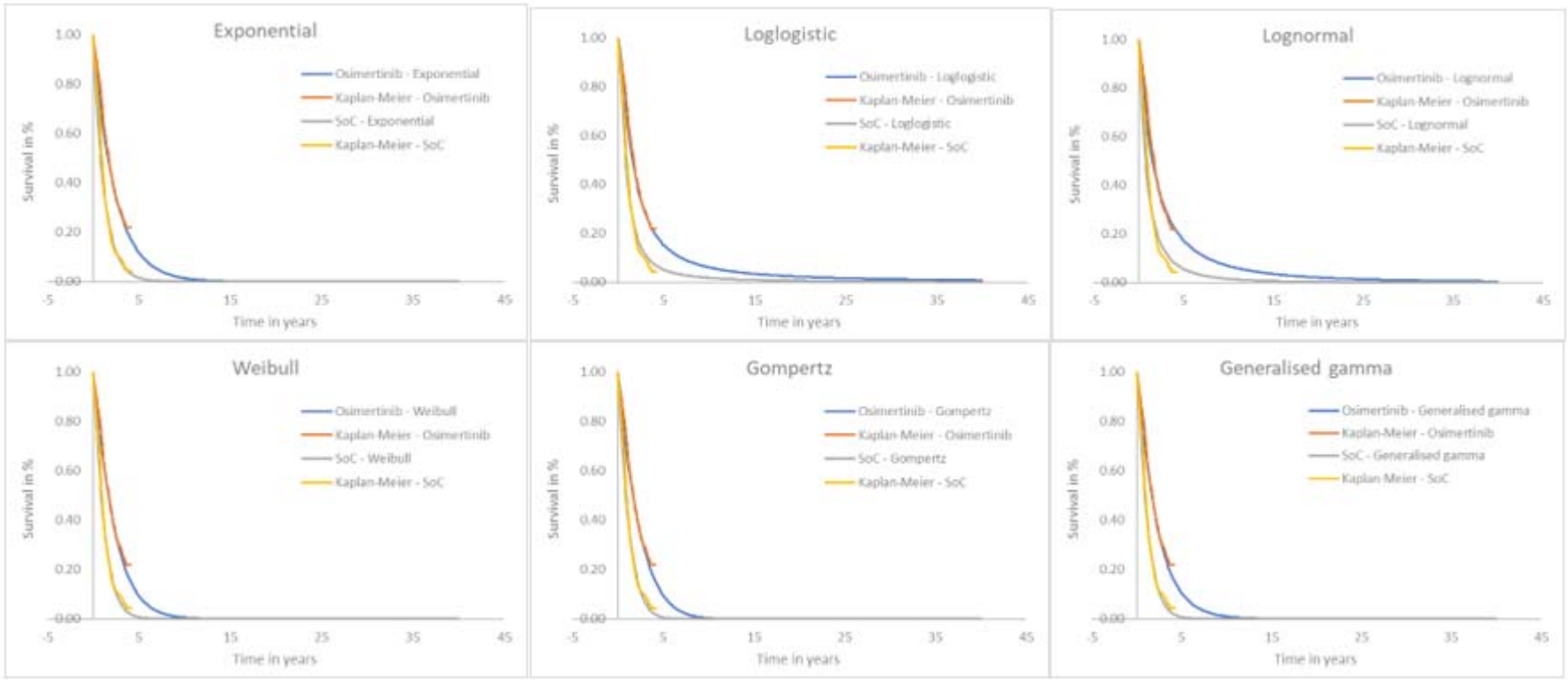


Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; TP6, transition probability 6.

Goodness of fit for parametric distributions

Individual parametric models were assessed for their goodness of fit based upon visual inspection and whether the extrapolation is clinically realistic. Figure 29 shows the fits and extrapolations for the transition from DM1 to DM2 (TP6), with the AIC and BIC values presented in Table 23. Based on visual inspection, the loglogistic and lognormal distributions appear optimistic, and are thus were considered as clinically implausible and 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 23) in both arms.

Figure 29: Extrapolation of DM1 to DM2 (TP6)



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

Table 23: Goodness of fit for DM1 to DM2

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

B.3.3.5.2 TP7: 1st line treatment of distant metastasis (DM1) to death

KM data

For the model's DM1 to death transition, combined KM data (based on pooled analysis of 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 30 applying the methods described below.

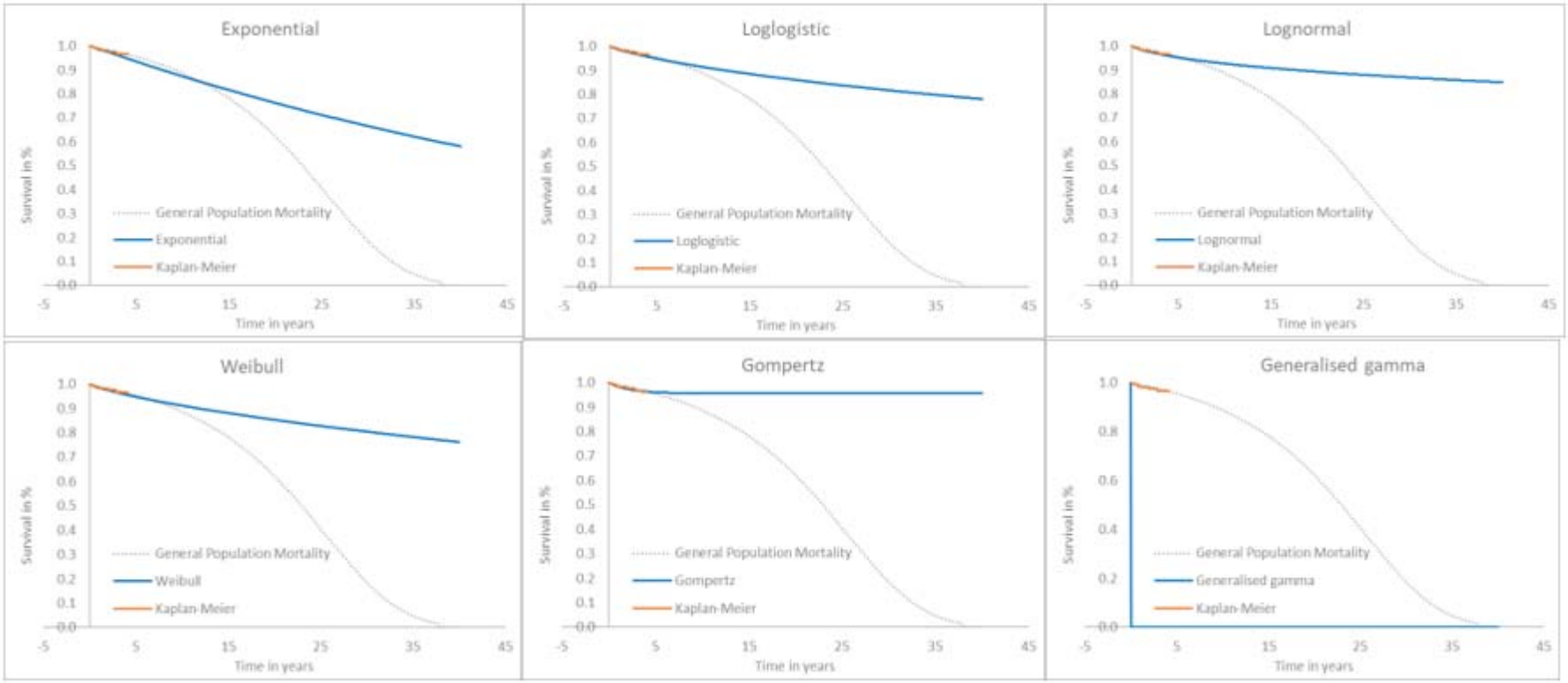
Figure 30: KM curves for the time to death (censoring discontinuation of treatment) using pooled data of both treatment arms of FLAURA

Abbreviation: KM, Kaplan-Meier.

Goodness of fit for parametric distributions

Parametric distributions were assessed for their goodness of fit based on visual inspection and whether the extrapolation is clinically realistic. Although the distribution as shown in Figure 31 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. 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 24); 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.

Figure 31: Extrapolation of DM1 to death (TP7)



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

Table 24: Goodness of fit for DM1 to death

		Placebo (active monitoring)	
Model	**Clinically viable**	**AIC**	**BIC**
Weibull	No	175.94	184.58
Generalised gamma	No	176.92	189.88
Gompertz	No	175.40	184.05
EXPONENTIAL	Yes	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.

B.3.3.5.3 TP8: 2nd line treatment of distant metastasis (DM2) to death

KM data

For the model's DM2 to death transition, KM data for the time from treatment discontinuation to death data from the FLAURA trial was used. Parametric curves were fitted to the separate treatment arms as presented in Figure 32, applying the methods described below.

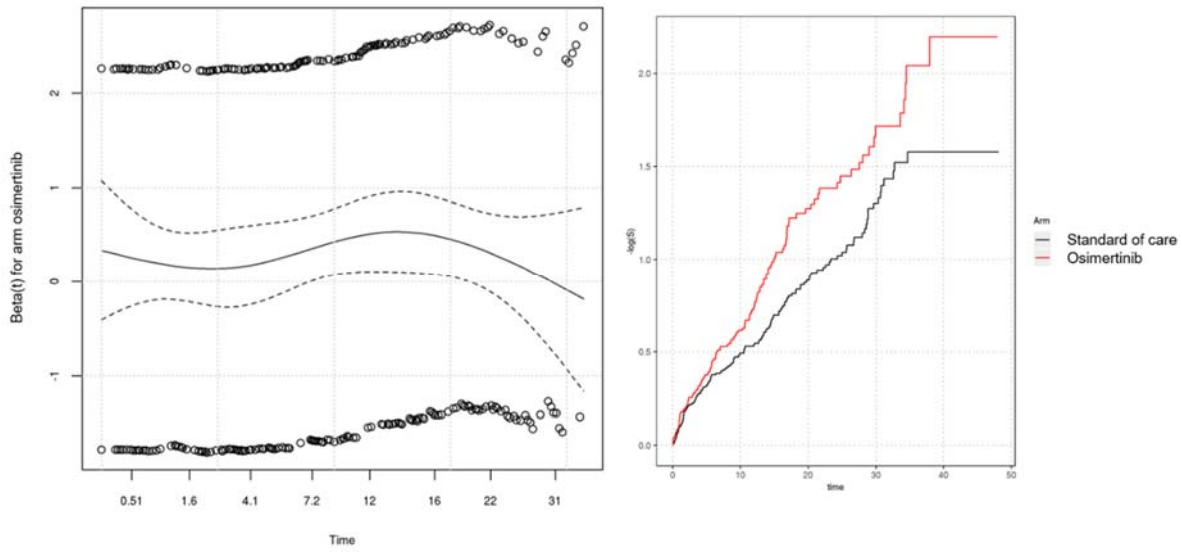
Figure 32: KM curves for post time to discontinuation of treatment in the osimertinib and SoC arms of FLAURA

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 33, with the statistical test results provided in Table 25. 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 does hold, 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. Again, for consistency with the parametric modelling based on the ADAURA DCO1 DFS data, individual fitted models were applied for the base case analysis.

Figure 33: Schoenfeld residuals and cumulative hazard plot for the transition DM2 to death (TP8)

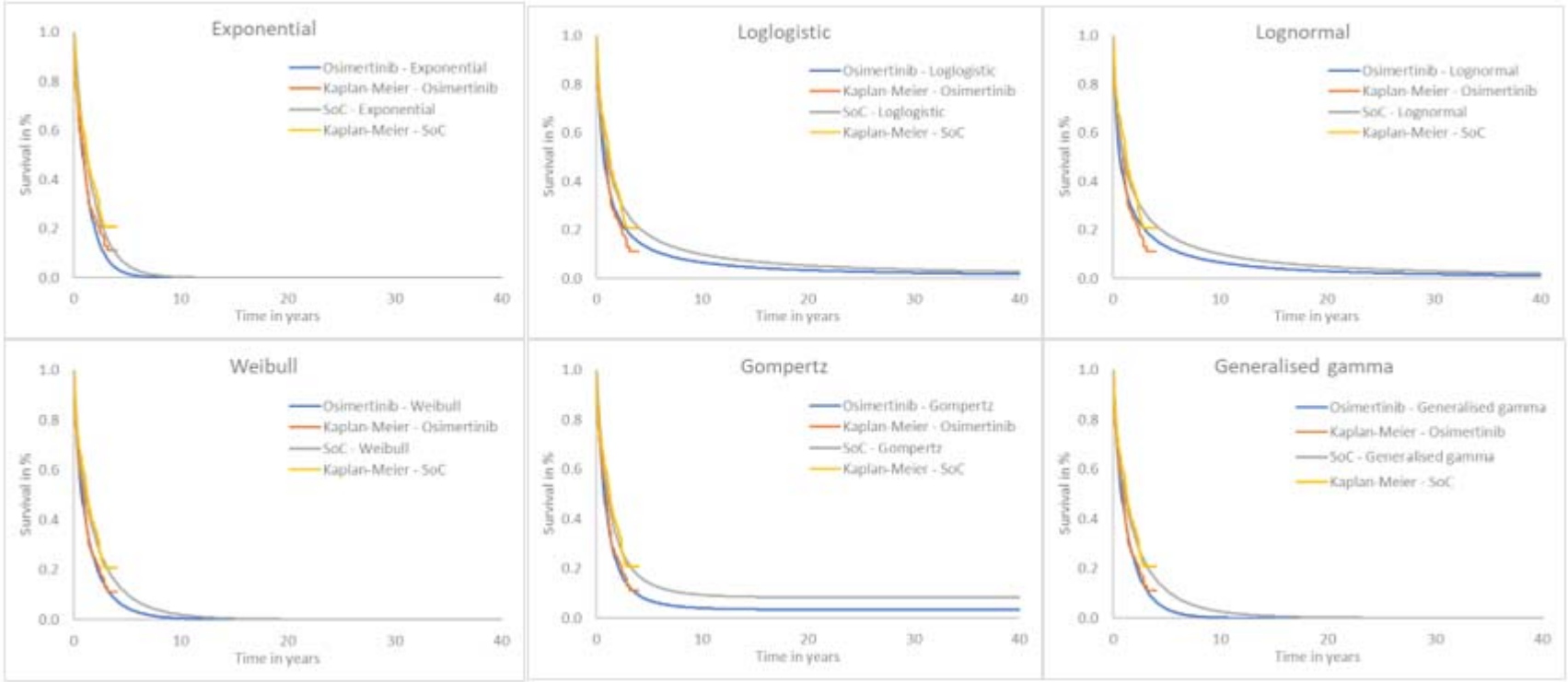


Left: Schoenfeld residuals plot; right: cumulative hazard plot.
Abbreviations: DM2, 2nd line distant metastasis; TP8, transition probability 8.

Goodness of fit for parametric distributions

Independent parametric distributions were assessed for their goodness of fit based on visual inspection and whether the extrapolation is clinically realistic. Figure 34 shows the fits and extrapolations for the transition from DM2 to death (TP8), with the AIC and BIC values provided in Table 25. US SEER Cancer Statistics Review with a long-term dataset (2010–2016) reports a 6.9% 5-year survival rate for the distant metastasis stage for NSCLC patients.[55] These data were used to compare the estimated 5-year survival rates produced by the extrapolated curves. The loglogistic and lognormal extrapolations for both the placebo (active monitoring) and osimertinib arms result in over 10% 5-year survival rates and thus they provide clinically implausible estimates compared to real-word evidence. Gompertz and exponential distributions also provide unrealistic curves by estimating very long and short tails of the survival curves, respectively. The distributions that estimated a similar 5-year survival rate for this patient population were the Weibull (placebo arm: 4.5%, osimertinib arm: 9.9%) and generalised gamma (placebo arm: 3.5%, osimertinib arm: 10.8%). However, based on statistical fit, the Weibull distribution provides the best fit and, therefore, this distribution was selected for the base case.

Figure 34: Extrapolation of DM2 to death (TP8)



Abbreviations: DM2, 2nd line distant metastasis; TP8, transition probability 8.

Table 25: Goodness of fit for DM2 to death

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

B.3.3.6 *Aggregated DFS and OS*

Reproducing the original endpoints of the modelled trial (ADAURA) is a key validation of a Markov model. The base case is set by using the parametric distributions with the best statistical fit and clinical plausibility for each transition, where for every possible combination of the parametric distribution in TP1 (DF to LRR) and TP2 (DF to 1L DM) the mean squared error (MSE) is calculated. Table 26 presents the ranking of all 36 combinations for both DFS and OS. As noted above the lognormal distribution was selected for TP1 and generalised gamma for TP2 and these curves appear to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each treatment arm. Among all 36 possible combinations, this combination was ranked 2nd in both DFS and OS in terms of MSE. This combination of distributions results in the aggregated DFS and OS shown in Figure 35 and Figure 36, respectively.

The base case parametric distributions applied for each transition are shown in Table 27. In addition, scenario analyses were also performed to test different curve selections.

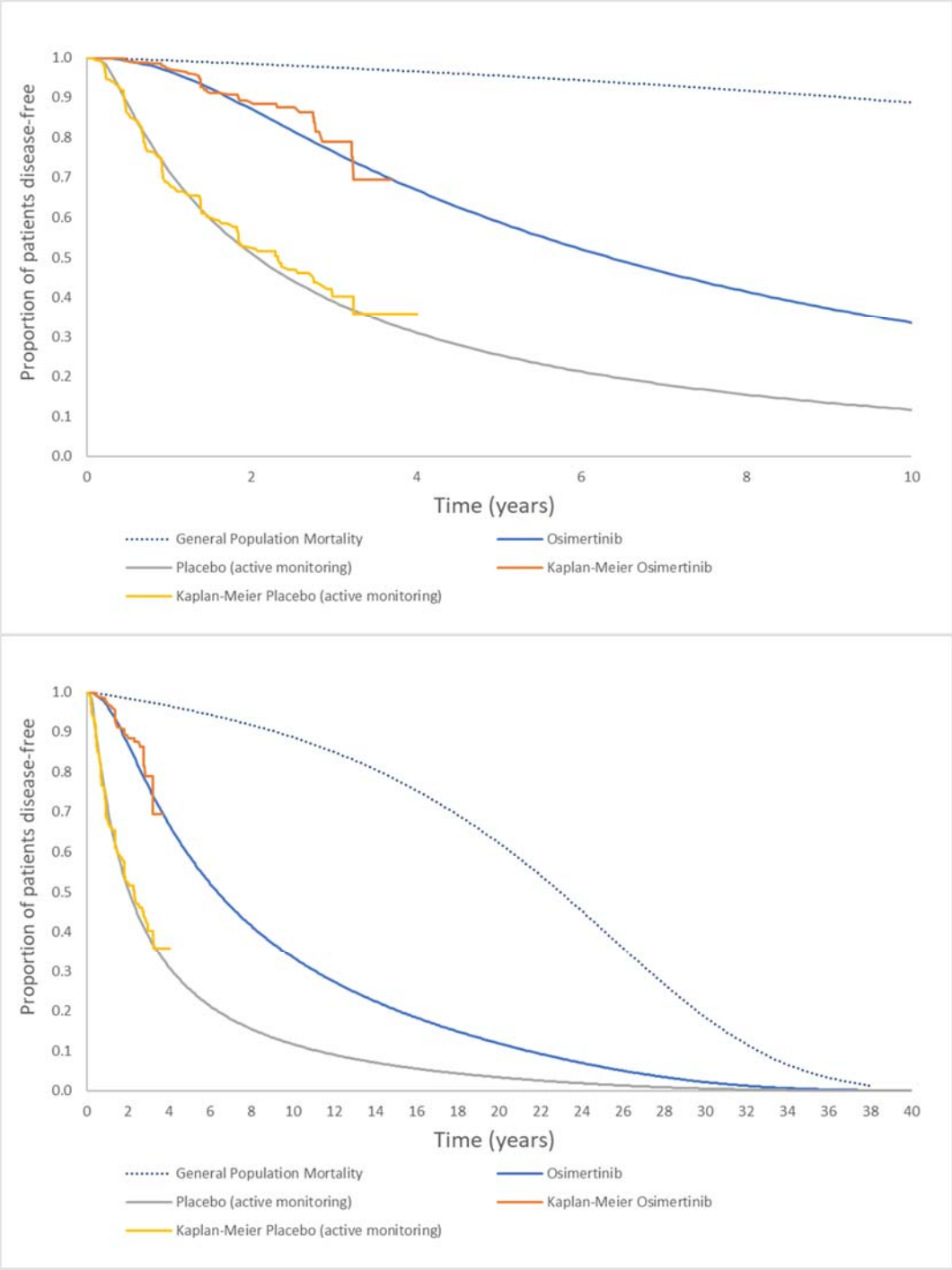
Table 26: Overview of the different combinations of fit for TP1 and TP2 and the resulting MSE

Combination	TP1	TP2	MSE DFS	MSE OS	MSE total
1	Generalised Gamma	Generalised Gamma	0.047928	0.288935	0.336862
2	Lognormal	Generalised Gamma	0.054964	0.288829	0.343793
3	Exponential	Generalised Gamma	0.049886	0.294461	0.344347
3	Exponential	Generalised Gamma	0.049886	0.294461	0.344347
4	Loglogistic	Generalised Gamma	0.063546	0.289551	0.353097
5	Gompertz	Generalised Gamma	0.061678	0.291792	0.35347
6	Weibull	Generalised Gamma	0.065665	0.289078	0.354743
7	Generalised Gamma	Lognormal	0.071649	0.295622	0.36727
8	Exponential	Lognormal	0.073898	0.301647	0.375545
9	Generalised Gamma	Gompertz	0.062162	0.317695	0.379858
10	Lognormal	Lognormal	0.08743	0.295446	0.382876

Combination	TP1	TP2	MSE DFS	MSE OS	MSE total
11	Generalised Gamma	Exponential	0.080278	0.308421	0.388699
12	Generalised Gamma	Weibull	0.086796	0.302793	0.389589
13	Lognormal	Gompertz	0.073196	0.317432	0.390628
14	Generalised Gamma	Loglogistic	0.086795	0.307629	0.394423
15	Gompertz	Lognormal	0.099655	0.298748	0.398403
16	Loglogistic	Lognormal	0.102242	0.296193	0.398435
17	Exponential	Gompertz	0.077789	0.323895	0.401685
18	Weibull	Lognormal	0.106527	0.295756	0.402283
19	Exponential	Weibull	0.094454	0.309159	0.403613
20	Lognormal	Exponential	0.09711	0.308086	0.405196
21	Loglogistic	Gompertz	0.08839	0.318137	0.406528
22	Exponential	Loglogistic	0.093258	0.313979	0.407236
23	Lognormal	Weibull	0.106746	0.302472	0.409218
24	Weibull	Gompertz	0.092021	0.3176	0.409621
25	Lognormal	Loglogistic	0.105467	0.307393	0.412859
26	Gompertz	Gompertz	0.095998	0.320747	0.416745
27	Loglogistic	Exponential	0.110149	0.308777	0.418927
28	Gompertz	Exponential	0.110589	0.311706	0.422295
29	Exponential	Exponential	0.107174	0.315348	0.422522
30	Weibull	Exponential	0.114828	0.308292	0.42312
31	Loglogistic	Weibull	0.125563	0.303171	0.428734
32	Loglogistic	Loglogistic	0.1232	0.308146	0.431346
33	Gompertz	Weibull	0.126039	0.305956	0.431995
34	Gompertz	Loglogistic	0.122826	0.310889	0.433715
35	Weibull	Weibull	0.131408	0.302708	0.434117
36	Weibull	Loglogistic	0.128195	0.3077	0.435894

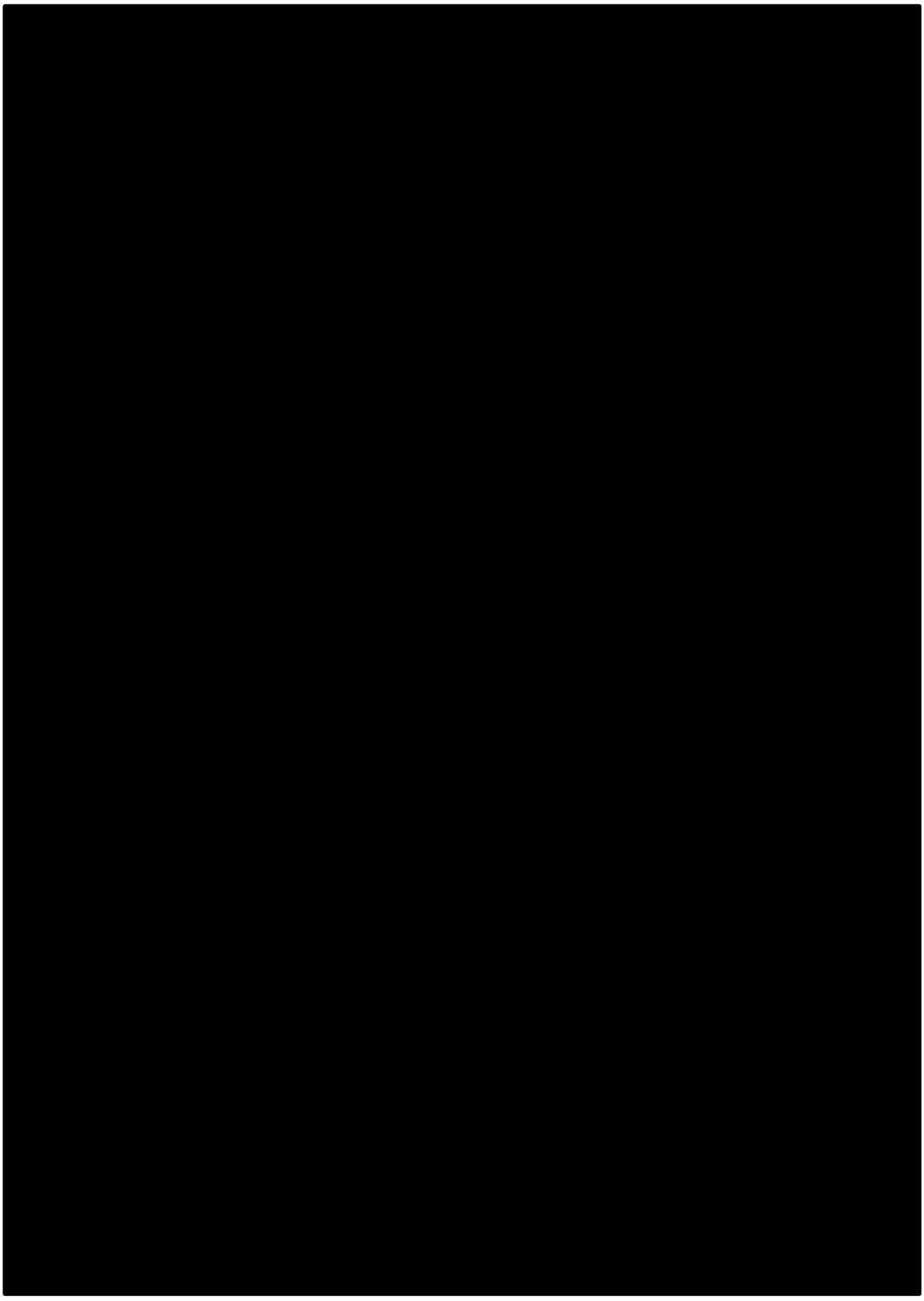
Abbreviations: DFS, disease-free survival; MSE, mean squared error; OS, overall survival; TP1, transition probability 1; TP2, transition probability 2.

Figure 35: Aggregated DFS without cure assumption applied compared with ADAURA DFS (10 and 40 year time horizon)



Abbreviation: DFS, disease-free survival

Figure 36: Aggregated OS without cure assumption applied compared with ADAURA OS (10 and 40-year time horizon)



Abbreviations: OS, overall survival

Table 27: Parametric distributions and data sources used for the base case transitions

Transition	Parametric distributions	Data source
TP1: DF → LRR	Lognormal	ADAURA [71]
TP2: DF → DM1	Generalised gamma	ADAURA [71]
TP3: DF → Death	Background mortality	UK life tables [87]
TP4: LRR → DM1	Lognormal	CancerLinQ[88]
TP5: LRR → Death	Background mortality	UK life tables[87]
TP6: DM1 → DM2	Weibull	FLAURA[89]
TP7: DM1 → Death	Exponential / background mortality	FLAURA[89]/UK life tables[87]
TP8: DM2 → Death	Weibull	FLAURA[89]

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

[redacted]

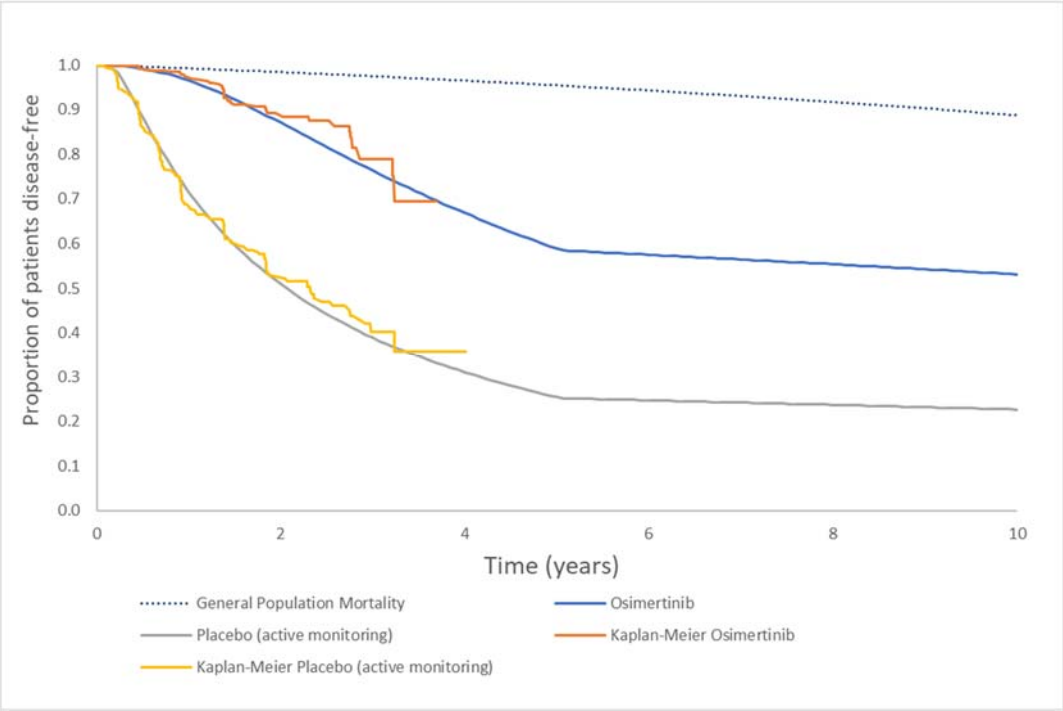
However, although the initial fit compared with the ADAURA KM is good for both DFS and OS, UK clinicians argued that long-term DFS and OS produced by initial extrapolation analyses presented to them were too pessimistic,[18] and that cure would expected; i.e. within a certain timeframe or landmark, a patient that has not experienced disease recurrence or death would be assumed effectively cured and discharged from active monitoring Their risk of dying would thus be similar to that of the general population, and thus application of general population background mortality to these patients would be a more clinically valid approach.[18]

Based on this feedback from clinicians, and in line with similar approaches in other NICE appraisals (as described in Section B.3.3.3.1), the base case assumes that 95% of patients surviving disease-free in Year 5 in either arm are functionally cured, and experience the age-adjusted general population mortality rate from this stage. This results in a DFS and OS curve that fits well compared with the ADAURA KM data, and shows a more clinically plausible survival estimate, as validated by UK clinical experts, in both arms (Figure 37 and Figure 38). A landmark comparison for the base case is presented in Table 28 and Table 29.

Comparing the model estimated DFS curves (Figure 37) with long-term published data, such as from the ANITA trial,[99] 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 placebo from ANITA are comparable as described in Section B.3.3.3.1. In terms of OS, at around 8 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; Figure 38) at those points in time.

Figure 37: Aggregated DFS curve based on the fitted KM data from ADAURA and applied cure assumption (95% cured after 5 years)



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

Table 28: Landmark comparison of aggregated DFS and ADAURA DFS (with cure assumption of 95% cured after 5 years)

	Osimertinib - model	ADAURA osimertinib	Placebo (active monitoring) - model	ADAURA placebo
Median DFS (months)	148.6	NR	24.9	27.5
% at 1 year	96.8%	[redacted]	72.7%	[redacted]
% at 2 years	87.4%	89.1%	51.6%	52.4%
% at 3 years	76.8%	[redacted]	39.3%	[redacted]
% at 4 years	67.2%	-	31.3%	-
% at 5 years	59.1%	-	25.6%	-
% at 10 years	53.2%	-	22.6%	-

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

Figure 38: Aggregated OS curve based on the fitted Kaplan-Meier data from ADAURA and applied cure assumption (95% cured after 5 years)

Abbreviations: OS, overall survival.

Table 29: Landmark comparison of aggregated OS and ADAURA OS (with cure assumption of 95% cured after 5 years)

	Osimertinib - model	ADAURA osimertinib	Placebo (active monitoring) - model	ADAURA placebo
Median OS (months)	175.3	[redacted]	83.1	[redacted]
% at 1 year	99.3%	[redacted]	98.8%	[redacted]
% at 2 years	98.0%	[redacted]	94.00%	[redacted]
% at 3 years	95.3%	[redacted]	85.9%	[redacted]
% at 4 years	90.6%	-	76.3%	-
% at 5 years	84.7%	-	66.5%	-
% at 10 years	60.9%	-	34.5%	-

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.3.3.7 *Clinical expert assessment of applicability of clinical parameters*

When OS and DFS curves produced by initial extrapolation analyses were presented to clinical experts, they found them extremely pessimistic compared to the outcomes they had observed in clinical practice within patients of this type, stating them to be more reflective of outcomes in the metastatic setting. In addition, the clinicians felt the extrapolations were

unrealistic given the unprecedented efficacy of osimertinib demonstrated in the ADAURA trial and the expectation of a functional cure after 5 years disease-free. Therefore, as discussed throughout in Section B.3.3, the chosen final models were selected based on a visual inspection of the combined DFS and OS curves, such that they achieve a good fit to the observed data and are deemed valid and realistic by UK clinical experts.[9, 18]

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). 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.[105] 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.

B.3.4.2 *Mapping*

SF-36 data from the osimertinib treatment arm of the ADAURA trial were the primary source of health state utility values (HSUVs). The EQ-5D-3L is the instrument preferred by NICE for the assessment of HRQoL, as stated in the NICE Guide to the methods of technology appraisal.[83] 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.

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,[106] which adheres to the guidance set out in NICE TSD 10.[107] Linear regression models were used to estimate the utilities using the generalised least squares (GLS) technique. As described in Rowen et al, 2009,[106] coefficients of the GLS model (model 3) with interaction terms were applied (SF-36 domains abbreviated). A list of the interaction terms are available in the full utility mapping report;[108] the EQ-5D utility score is the dependent variable. To obtain utility scores, UK-specific preference weights were used to calculate utility values.[109] Observations with missing data were excluded from the analyses, [redacted].[71]

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.[110] 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.[111]

Prior to data analysis, validation checks were performed. In the ADAURA trial, there were 682 patients (339 receiving osimertinib; 343 receiving placebo), [redacted]. These numbers were also found in the data required for analysis and thus passed the validation checks. [redacted]

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.[108]

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

B.3.4.2.2 Results of Mapping analysis

As shown in Figure 39 and Table 30, 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 at the EOT, likely explained by the fact that there are fewer patients within each arm (111 and 65 for placebo (active monitoring) and osimertinib, respectively).

Figure 39: Mean EQ-5D scores from ADAURA (all observations)

Abbreviations: EOT, end of treatment.

Table 30: 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]

	Tx	*n*	Mean utility	SD
144 weeks	Placebo	[redacted]	[redacted]	[redacted]
	Osimertinib	[redacted]	[redacted]	[redacted]
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 31. 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 31: 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

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 32. 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 32. 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 33), 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 34 outlines the parameter estimates obtained using model 3.

Table 33. 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 34. 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 35.

Table 35: 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,[106] 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.

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 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.[29, 46, 112-115] Of these, three studies were RCTs that investigated the impact of adjuvant chemotherapy or gefitinib on HRQoL over time.[46, 112, 114] 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. [29] All studies considered patients with early stage, resected NSCLC, although one study was further restricted to stage IB–II disease.[46]

The cancer-specific EORTC-QLQ tool was frequently used to measure HRQoL, including the Q30 in two studies,[46, 114] 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,[29] and were described using the generic preference-based EQ-5D instrument. Andreas et al, 2018,[29] 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).[29] 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.3.4.4 *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,[29] 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,[29] are somewhat lower than the base case utility scores estimated from ADAURA and used for this appraisal (Table 36), 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,[29] was nevertheless conducted to explore the impact of using different utilities, with results presented in Section B.3.8.3.

Table 36: Comparison of DF HSUVs

	ADAURA	Andreas et al, 2018[29]
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,[116] and NICE TA653.[117] The study by Nafees et al, 2008,[116] 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.[117] 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 lilkely 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 37.

Table 37: Summary of AE related disutility values applied in cost-effectiveness analysis

AE	Disutility	Frequency	
		Osimertinib	Placebo (active monitoring)
Paronychia	−0.0325	0.9%	0%
Decreased Appetite	−0.05	0.6%	0%
Diarrhoea	−0.0468	1.8%	0.3%
Stomatitis *	−0.05	1.5%	0%

AE	Disutility	Frequency	
		Osimertinib	Placebo (active monitoring)
ECG QT prolonged **	0	0.9%	0.3%

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 was 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.1.3.2.2), 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).[45] 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,[44] 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, HRQoL data were obtained from the FLAURA trial, which assessed osimertinib as first-line treatment for patients with previously untreated, EGFR mutation–positive advanced NSCLC. Utility values from progression-free patients in FLAURA 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,[118] 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).[90] 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.[119]

All utility values used in the base case model are presented in Table 38. Scenario analyses were conducted using the utility values reported by Andreas et al, 2018.[29]

Table 38: 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 [71]
DF: Placebo (active monitoring)	[redacted]	0.018	B.3.4.2	ADAURA [71]
LRR: Osimertinib	[redacted]	0.018	B.3.4.2	ADAURA [71]
LRR: Placebo (active monitoring)	[redacted]	0.018	B.3.4.2	ADAURA [71]
DM1: Osimertinib	0.794	0.0069	B.3.4.6	FLAURA [89]
DM1: Placebo (active monitoring)	0.794	0.0069	B.3.4.6	FLAURA [89]
DM2	0.640	0.03	B.3.4.6	Labbé et al, 2017 [119]

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.[120]

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.[18] 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.[90]

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.

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.[29, 121-123] All four studies were retrospective in nature; three considered patients with stage IB−IIIA NSCLC,[29, 122, 123] while Ahmad et al, 2017,[121] 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.[29] The LuCaBIS study by Andreas et al, 2018,[29] 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.3.5.1.1 Appropriateness of NHS Ref costs/PbR tariffs

NHS reference costs for 2018/19 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.[124]

B.3.5.1.2 Clinical expert assessment of applicability of cost and healthcare resource use values

Expert opinion was sought from six UK clinicians to validate the applicability of the healthcare resource use data to UK clinical practice.[18] 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,[29] 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.[125] Finally, although additional surgery is included as an option in the clinical pathway for patients who have LRR (Figure 4), 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

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 uncertain. Despite this, the six UK clinical experts interviewed advised that they would consider retreatment with osimertinib provided a patient was considered to have successfully completed adjuvant treatment with osimertinib: that is, 3 years treatment and at least 2 years free from progression to LRR or metastatic disease.[18] The clinicans 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 5 years (60 months) from model entry would be retreated with osimertinib on entry to the DM1 health state, and the remainder (50%) would receive PDC. In addition, the 5-year retreatment time point was selected as feedback from interviews with clinicians suggested patients are most at risk of recurrence within 18–24 months post-surgery.[18] Therefore, the model applies a conservative assumption by adding the 18 to 24-month risk period to the end of the three-year treatment duration (i.e. 5 years from surgery). The 5-year retreatment time point also aligns with the 5-year time point for cure creating alignment and internal consistency in the model. However, scenario analyses are also provided exploring the impact of retreatment at 4 and 6 years in the model and the percentage of patients retreated with osimertinib.

Table 39 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 and thus the subsequent anti-cancer therapies reported in the trial (Appendix P), which is based on immature data, were not specifically reflective of UK practice,[71] the subsequent therapies included in the model were based on current and expected clinical practice in the UK based on clinical opinion.[18]

For the estimation of osimertinib costs in DF (initial use), 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 40). 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. 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 40: Time to treatment discontinuation from ADAURA

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.[126-129] These treatment cycles were adjusted to the cycle length (i.e. 28 days) in the model. 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 28 days based on NICE guidelines.[3] Osimertinib retreatment was given until progression (in the model that is 481 model cycles, which is then adjusted for the average time to progression) based on the FLAURA trial data used in the DM survival modelling.[89]

Table 39: 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. 38 model cycles])	Placebo (active monitoring)
LRR	PDC + radiotherapy (3 model cycles or until progression)	PDC + radiotherapy (3 model cycles or until progression)
DM1	Enter DM1 <60 months after initiating adjuvant osimertinib: • PDC: 100% (3.8 model cycles or until progression) Enter DM1 ≥60 months after initiating adjuvant osimertinib: • Osimertinib retreatment: 50% (until progression) • PDC: 50% (3.8 model cycles or until progression)	Osimertinib (until progression)
DM2	If retreated with osimertinib in DM1: PDC (3.8 model cycles or until death) If not retreated with osimertinib in DM1 (i.e. received PDC): Docetaxel (3 model cycles or until death)	PDC (3.8 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 40. Where multiple generic forms of a drug were available, the cheapest generic form was used for the base case. Due to confidential pricing arrangements for osimertinib, the base case [redacted].

Table 40: Drug acquisition costs

Drug	Vial size/ tablet dose	Pack size	Cost per pack	Source
Osimertinib [redacted]	80 mg	30	[redacted] (list price: £5,770.00)	AZ data on file BNF 2020 [130]
Osimertinib [redacted]	80 mg	30	[redacted] (list price: £5,770.00)	AZ data on file BNF 2020 [130]

Drug	Vial size/ tablet dose	Pack size	Cost per pack	Source
PDC: Pemetrexed	100 mg	1	£125.00	BNF 2020 [130]
PDC: Cisplatin	50 mg	1	£4.12	eMIT 2019 [131]
Docetaxel	80 mg	1	£51.00	BNF 2020 [130]

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 41.

Table 41: Radiotherapy unit cost

Resource	Unit cost	Source[124]
Radiotherapy fraction	£2,632.56	NHS Reference costs 2018/19: SC30Z - Deliver a Fraction of Intraluminal Brachytherapy

Abbreviations: NHS, National Health Service.

B.3.5.2.3 Dosing

Drug dosing and acquisition costs per model cycle are presented in Table 42. 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.[90] 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 28-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.[132] 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 42: 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 (without wastage)	Cost per model cycle (with wastage)
TKI						
Osimertinib [redacted]	80 mg	30	30	98.9%§	[redacted]	[redacted]
Osimertinib [redacted]	80 mg	30	30	98.9%§	[redacted]	[redacted]
PDC						
Pemetrexed	500 mg/m^2	1	21	100%‡	£1,391.67	£1,500.00
Cisplatin	75 mg/m^2	1	21	100%‡	£13.76	£16.48
Single chemotherapy						
Docetaxel	75 mg/m^2	1	21	100%‡	£106.46	£136.00

Abbreviations: PDC, pemetrexed, cisplatin; TKI, tyrosine kinase inhibitor.
† Assumption – Equivalent to SoC in FLAURA; ‡ Assumption; § FLAURA trial.

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,[133] based on 12 minutes of pharmacist time to align with the ERG's recommendations in TA654.[90] Chemotherapy administration costs (for pemetrexed, cisplatin and docetaxel) were sourced from NHS Reference costs 2018/19, considering an outpatient attendance for delivery of 'complex chemotherapy including prolonged infusional treatment'.[124] 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,[131] was added to the administration cost of chemotherapy treatments. The drug administration costs applied in the model are described in Table 43.

Table 43: Drug administration costs

Drug	Administration	Unit cost	Cost per first administration	Cost per subsequent administration	Source
Osimertinib	Band 6 pharmacist dispensing (12 mins)	£45 per hour	£9.00	£9.00	PSSRU 2019[133]
PDC, cisplatin or pemetrexed	Deliver complex chemotherapy, including prolonged infusional treatment – outpatient (SB14Z) – First attendance	£371.00	£372.27	£333.40	NHS Reference costs 2018/19[124]
	Deliver Subsequent Elements of a Chemotherapy Cycle - SB15Z	£332.10			NHS Reference costs 2018/19[124]
	Dexamethasone (premedication), 8 mg per day for 3 days, £12.71	£12.71 per 30 x 8 mg pack			eMIT 2019[131]
Docetaxel	Deliver complex chemotherapy, including prolonged infusional treatment – outpatient (SB14Z) – First attendance	£371.00	£373.54	£334.67	NHS Reference costs 2018/19[124]

Drug	Administration	Unit cost	Cost per first administration	Cost per subsequent administration	Source
	Deliver Subsequent Elements of a Chemotherapy Cycle - SB15Z	£332.10			NHS Reference costs 2018/19[124]
	Dexamethasone (premedication), 16 mg per day for 3 days, £12.71	£12.71 per 30 x 8 mg pack			eMIT 2019[131]

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 2018/19,[124] were applied in each model cycle to patients on the PDC regimen or on docetaxel alone, according to the EMA label information. As no details on the frequency of these tests are included in the labels, it was assumed that all tests were conducted once every treatment cycle (Table 44).

Treatment with osimertinib does not require any monitoring tests and thus relevant costs were not included.

Table 44: Monitoring costs for PDC regimen

Chemotherapy regimen	Test	Unit cost	Cost per treatment cycle	Source [124]
PDC	Liver function test	£1.10	£4.99	DAPS04 – Clinical biochemistry
	Renal function test	£1.10		DAPS04 – Clinical biochemistry
	Complete blood count	£2.79		DAPS05 – Haematology
Docetaxel	Complete blood count	£2.79	£2.79	DAPS05 – Haematology

Abbreviations: PDC, pemetrexed, cisplatin.

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,[29] 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,[18] and resource use estimates per cycle are presented in Table 45.

For the DF health state, Andreas et al, 2018 [29] 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, 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.[18] The values from Andreas et al. 2018 were amended accordingly. As radiotherapy is only applied in the model as part of chemoradiotherapy to patients in the LRR group (Section B.3.5.2.1), radiotherapy resource use was not included for any health state costs as part of disease management costs in the model. 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 5-year 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 [29] did not distinguish between these patient groups (Table 45). 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 2018/19[124] and are presented in Table 46. A summary of the total health state costs is provided in Table 47.

Table 45: Healthcare resource use, by health state

	Healthcare resource use per 28-day cycle[29]			
	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

	Healthcare resource use per 28-day cycle[29]			
	DFS†	Loco-regional recurrence	1st line distant metastases	2nd line distant metastases
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 46: Healthcare resource use unit costs

Resource	Unit cost	Source[124]
Hospitalisation	£598.73	NHS Reference costs 2018/19: 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)	£148.95	NHS Reference costs 2018/19: 800 - Clinical Oncology (Previously Radiotherapy) consultant led outpatient attendance
Surgeon visits	£205.89	NHS Reference costs 2018/19: 173 - Thoracic Surgery consultant led outpatient attendance
Pulmonologist/ respiratory physician (subsequent)	£163.62	NHS Reference costs 2018/19: 340 - Respiratory medicine consultant led outpatient attendance
Other specialist visit	£148.95	Assuming it costs the same as a visit to a clinical oncologist: 800 - Clinical Oncology (Previously Radiotherapy) consultant led outpatient attendance
A&E visits	£174.15	NHS Reference costs 2018/19: 180 - Accident & Emergency consultant led outpatient attendance
CT scans	£103.61	NHS Reference costs 2018/19: RD24Z - Computerised Tomography Scan of two areas, with contrast
MRI	£204.35	NHS Reference costs 2018/19: RD05Z - Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
PET scans	£829.61	NHS Reference costs 2018/19: RN07A - Positron Emission Tomography (PET), 19 years and over

Resource	Unit cost	Source[124]
PET-CT scans	£520.37	NHS Reference costs 2018/19: 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	£82.37	NHS Reference costs 2018/19: RD41Z/RD43Z - Ultrasound Scan with duration of less than 20 minutes/20 minutes and over, with Contrast (weighted average)
Nuclear medicine studies	£194.20	NHS Reference costs 2018/19: 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 47: Healthcare resource use, cost per health state per model cycle

Health state	Cost
DF	£241.89
LRR	£487.64
DM1	£655.47
DM2	£655.47

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

In the ADAURA trial, [redacted] of patients who experienced disease recurrence in the osimertinib and in the placebo (active monitoring) arms,[71] respectively, had CNS metastasis. Therefore, 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 48). Resource use frequencies were sourced from NICE TA536,[125] adjusted for the baseline DM resource use and costs described above and the 28-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[124] and PSSRU 2019[133] 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[125] and six UK clinicians interviewed for this appraisal)[18] and a publication by the Royal College of Radiologists, 2019,[134] 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 49).

Table 48: Additional healthcare resource use and costs associated with CNS metastasis

Resource	Frequency per cycle	Unit cost	Source
Consultant/Oncologist outpatient visit	0.5	£148.95	NHS Reference costs 2018/19: 800 - Clinical Oncology (Previously Radiotherapy) consultant led outpatient attendance [124] NICE TA536 (ID925) [125]

Resource	Frequency per cycle	Unit cost	Source
GP visit	0.9	£39.00	PSSRU 2019: GP consultation lasting 9.22 minutes (with qualification costs) [133] NICE TA536 (ID925) [125]
Cancer nurse visit	1.4	£98.74	NHS Cost collection 2018/19: N10AF - Specialist Nursing, Cancer Related, Adult, Face to face [124] NICE TA536 (ID925) [125]
Full blood test	1.4	£2.79	NHS Cost collection 2018/19: DAPS05 – Haematology [124] NICE TA536 (ID925) [125]
Biochemistry	1.4	£1.10	NHS Cost collection 2018/19: DAPS04 – Clinical biochemistry [124] NICE TA536 (ID925) [125]
CT scan	0.4	£115.19	NHS Cost collection 2018/19: RD26Z - Computerised Tomography Scan of three areas, with contrast [124] NICE TA536 (ID925) [125]
MRI scan	0.3	£204.35	NHS Cost collection 2018/19: RD05Z - Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast [124] NICE TA536 (ID925) [125]
X-ray	0.5	£30.59	NHS Cost collection 2018/19: DAPF - Direct Access Plain Film [124] NICE TA536 (ID925) [125]
Total	**-**	**£386.87**	

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

Table 49: Radiotherapy costs in CNS metastasis

Radiotherapy approach	% of patients	Doses	Unit cost	Source
Stereotactic radiotherapy	50%	6	£3,084.42	Royal College of Radiologists 2019 [134] NHS Reference costs 2018/19: AA71A-B - Stereotactic Intracranial Radiosurgery, for Neoplasms or Other Neurological Conditions, with CC Score 0-4+; Elective (weighted average) [124]
Whole brain radiotherapy	50%	1	£4,302.06	Royal College of Radiologists 2019 [134] ERG report for NICE ID925 (TA536)† [125]

Abbreviations: CNS, central nervous system; ERG, Evidence review group; NHS, National Health Service.
† Inflated from 2017 to 2019, 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 50). 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.[135] Cost inputs were sourced from NHS Reference costs 2018/19,[124] the PSSRU 2019,[133] and a Marie Curie report.[136]

Table 50: Terminal care costs

Terminal care in:	% of patients[135]	Unit cost	Source
Hospital	55.8%	£2,265.49	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 2018/19 [124]
Hospice	16.9%	£2,831.86	Assuming 25% increase on hospital inpatients care
Home	27.3%	£1,747.52	28 hours community nurse visit including travel time: N02AF - District Nurse, Adult, Face to face (NHS Reference Costs 2018/19; £39.68 per hour) [124] 7 GP home visits including travel time: Per patient contact lasting 9.22 minutes including carbon emissions (incl. qualification and direct staff costs) (PSSRU 2019; £39.23) [133] Drugs and equipment - Marie Curie report figure of £240 (2003/04) [136] updated to 2018/19 value using HCHS and NHSCII from PSSRU 2010 and 2019 [133]
Total	**-**	**£2,219.80**	

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 3–4 treatment-related 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, five 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 sourced from the NHS Reference Costs 2018/19 (Table 51).[124]

Table 51: Adverse event costs

Grade 3-4 adverse event	Incidence[71]		Cost input	Source[124]
	Osimertinib	Placebo (active monitoring)		
Paronychia	0.9%	0.0%	£1,509.22	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%	£1,987.00	Nutritional Disorders with/without Interventions, with CC Score 0–2+; Non-elective long and short stay (weighted average)
Diarrhoea	1.8%	0.3%	£1,396.32	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%	£853.18	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	0.9%	0.3%	£1,739.85	Other Acquired Cardiac Conditions with CC Score 0–13+; Non-elective long and short stay (weighted average)

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

B.3.5.5 *Miscellaneous unit costs and resource use*

A one-off EGFR mutation testing cost was applied in the first model cycle to all patients on osimertinib, and as a one-off cost for patients in the placebo (active monitoring) arm who received osimertinib on progression to the DM1 health state.

The cost of an EGFR test was sourced from the Diagnostic Assessment Report produced for NICE DG9 for EGFR-TK mutation testing in adults with locally advanced or metastatic NSCLC.[58] The DG9 report provides the prices of individual EGFR tests including purchase costs, personnel, materials and overheads. In addition, it reports the results of a survey of NHS laboratories which found that the Therascreen® EGFR PCR kit was the most commonly used EGFR mutation test. Therefore, and in line with the approach taken in NICE TA192,[63] the price of Therascreen® was used to represent the cost of EGFR testing. As a conservative approach, the most expensive price for a Therascreen® test listed in the DG9 report was used (£190) and inflated to current value (£208.98).[133]

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 52. The confidence intervals and distributions used to vary these parameters in the sensitivity analyses are provided in Appendix M.

Table 52: 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.3.5.2.3	UK population combined with the Gehan and George formula (0.01545*(height^0.54468)*(weight^0.46336))
Osimertinib retreatment timepoint	5 years	Varied in scenario analyses	B.3.5.2	Expert clinical opinion
Osimertinib retreatment percentage	50%	Varied in scenario analyses	B.3.5.2	Assumption
Survival distributions				
DF to LRR (TP1) - Osimertinib	Lognormal	Cholesky decomposition	0	ADAURA
DF to LRR (TP1) – Placebo (active monitoring)	Lognormal	Cholesky decomposition	0	ADAURA
DF to DM1 (TP2) - Osimertinib	Generalized Gamma	Cholesky decomposition	B.3.3.3.3	ADAURA
DF to DM1 (TP2) – Placebo (active monitoring)	Generalized Gamma	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.3.3.4.1	CancerLinQ
LRR to DM1 (TP4) – Placebo (active monitoring)	Lognormal	Cholesky decomposition	B.3.3.4.1	CancerLinQ
LRR to Death (TP5) - Osimertinib	Exponential	Cholesky decomposition	B.3.3.4.2	UK Life Table
LRR to Death (TP5) – Placebo (active monitoring)	Exponential	Cholesky decomposition	B.3.3.4.2	UK Life Table
DM1 to DM2 (TP6) - Osimertinib	Weibull	Cholesky decomposition	B.3.3.5.1	FLAURA
DM1 to DM2 (TP6) - Placebo	Weibull	Cholesky decomposition	B.3.3.5.1	FLAURA
DM1 to Death (TP7) - Osimertinib	Exponential	Cholesky decomposition	B.3.3.5.2	FLAURA / UK Life Table
DM1 to Death (TP7) – Placebo (active monitoring)	Exponential	Cholesky decomposition	B.3.3.5.2	FLAURA / UK Life Table
DM2 to Death (TP8) - Osimertinib	Weibull	Cholesky decomposition	B.3.3.5.3	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.3.3.5.3	FLAURA
Cure parameters				
Cure timepoint	5 years	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	Yes	Fixed	B.3.5.2.3	Assumption
DF: Osimertinib	[redacted]	Gamma ([redacted])	B.3.5.2	AZ data on file
LRR: Chemoradiotherapy	£6,431	Gamma (643.09)	B.3.5.2	NHS Reference Costs 2018/19, BNF 2020, eMIT
DM1				
No retreatment: PDC	£925	Gamma (92.46)	B.3.5.2	BNF 2020, eMIT
Retreatment: Osimertinib	[redacted]	Gamma ([redacted])	B.3.5.2	AZ data on file
DM2				
Received osimertinib at DM1: PDC	£1,405	Gamma (140.5)	B.3.5.2	BNF 2020, eMIT
Received PDC at DM1: Docetaxel	£37	Gamma (3.7)	B.3.5.2	BNF 2020
Drug acquisition costs (per model cycle), placebo (active monitoring) arm				
DF: Placebo (active monitoring)	£0	Gamma (0)	B.3.5.2	-
LRR: Chemoradiotherapy	£4,142	Gamma (414.2)	B.3.5.2	NHS Reference Costs 2018/19, BNF 2020, eMIT

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
DM1: Osimertinib	[redacted]	Gamma ([redacted])	B.3.5.2	AZ data on file
DM2: PDC	£435	Gamma (43.5)	B.3.5.2	BNF 2020, eMIT
Administration costs per model cycle				
First cycle				
Osimertinib	£8.40	Gamma (0.84)	B.3.5.2	PSSRU 2019
Docetaxel	£501.78	Gamma (50.18)	B.3.5.2	NHS Reference Costs 2018/19
PDC	£503.01	Gamma (50.30)	B.3.5.2	NHS Reference Costs 2018/19
Subsequent cycles				
Osimertinib	£8.40	Gamma (0.84)	B.3.5.2	PSSRU 2019
Docetaxel	£449.95	Gamma (44.995)	B.3.5.2	NHS Reference Costs 2018/19
PDC	£451.19	Gamma (45.12)	B.3.5.2	NHS Reference Costs 2018/19
Adverse event costs (per event)				
Paronychia	£1,509.22	Gamma (150.92)	B.3.5.4	NHS Reference costs 2018/19
Decreased appetite	£1,987.00	Gamma (198.70)	B.3.5.4	NHS Reference costs 2018/19
Diarrhoea	£1,396.32	Gamma (139.63)	B.3.5.4	NHS Reference costs 2018/19
Stomatitis	£853.18	Gamma (85.32)	B.3.5.4	NHS Reference costs 2018/19
ECG QT prolonged	£1,739.85	Gamma (173.99)	B.3.5.4	NHS Reference costs 2018/19
Adverse events (%)				
Osimertinib				
Paronychia	0.9%	Beta (0.0009)	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
Decreased appetite	0.6%	Beta (0.0006)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Diarrhoea	1.8%	Beta (0.0018)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Stomatitis	1.5%	Beta (0.0015	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
ECG QT prolonged	0.9%	Beta (0.0009)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Placebo (active monitoring)				
Paronychia	0%	Beta (0)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Decreased appetite	0%	Beta (0)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Diarrhoea	0.3%	Beta (0.0003)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Stomatitis	0%	Beta (0)	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	0.3%	Beta (0.0003)	B.3.5.4	ADAURA CSR Table 14.3.2.5 (Safety analysis set)
Utilities				
Osimertinib (DF)	[redacted]	Beta (0.018)	B.3.4.6	ADAURA
Placebo (active monitoring) (DF)	[redacted]	Beta (0.018)	B.3.4.6	ADAURA
Osimertinib (LRR)	[redacted]	Beta (0.009)	B.3.4.6	ADAURA
Placebo (active monitoring) (LRR)	[redacted]	Beta (0.009)	B.3.4.6	ADAURA
Osimertinib (DM1)	0.794	Beta (0.0069)	B.3.4.6	FLAURA
Placebo (active monitoring) (DM1)	0.794	Beta (0.0069)	B.3.4.6	FLAURA
DM2	0.64	Beta (0.03)	B.3.4.6	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
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

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
HCRU costs per cycle				
DF				
Hospitalisation	£41.31	Gamma (4.13)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Oncologist visits (subsequent)	£12.77	Gamma (1.28)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Surgeon visits	£30.99	Gamma (3.10)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Pulmonologist/ respiratory physician (subsequent)	£24.97	Gamma (2.50)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Other specialist visit	£21.73	Gamma (2.17)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Emergency room	£11.29	Gamma (1.13)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
CT scans	£8.23	Gamma (0.82)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
MRI	£8.97	Gamma (0.90)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET scans	£38.16	Gamma (3.82)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET-CT scans	£33.73	Gamma (3.37)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Ultrasound	£5.68	Gamma (0.57)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Nuclear medicine studies	£4.06	Gamma (0.41)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Loco-regional recurrence				
Hospitalisation	£71.60	Gamma (7.16)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Oncologist visits (subsequent)	£94.55	Gamma (9.45)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Surgeon visits	£37.88	Gamma (3.79)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Pulmonologist/ respiratory physician (subsequent)	£39.13	Gamma (3.91)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Other specialist visit	£34.26	Gamma (3.43)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Emergency room	£20.83	Gamma (2.08)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
CT scans	£20.97	Gamma (2.10)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
MRI	£76.32	Gamma (7.63)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET scans	£47.87	Gamma (4.79)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET-CT scans	£7.58	Gamma (0.76)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Ultrasound	£17.86	Gamma (1.79)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Nuclear medicine studies	£18.80	Gamma (1.88)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
DM1				
Hospitalisation	£123.93	Gamma (12.39)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Oncologist visits (subsequent)	£90.78	Gamma (9.08)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Surgeon visits	£30.78	Gamma (3.08)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Pulmonologist/ respiratory physician (subsequent)	£18.81	Gamma (1.88)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Other specialist visit	£22.27	Gamma (2.23)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Emergency room	£28.04	Gamma (2.80)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
CT scans	£27.40	Gamma (2.74)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
MRI	£28.20	Gamma (2.82)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET scans	£190.79	Gamma (19.08)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET-CT scans	£59.84	Gamma (5.98)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Ultrasound	£12.31	Gamma (1.23)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Nuclear medicine studies	£22.33	Gamma (2.23)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
DM2				
Hospitalisation	£123.93	Gamma (12.39)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Oncologist visits (subsequent)	£90.78	Gamma (9.08)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Surgeon visits	£30.78	Gamma (3.08)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Pulmonologist/ respiratory physician (subsequent)	£18.81	Gamma (1.88)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Other specialist visit	£22.27	Gamma (2.23)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Emergency room	£28.04	Gamma (2.80)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
CT scans	£27.40	Gamma (2.74)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
MRI	£28.20	Gamma (2.82)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET scans	£190.79	Gamma (19.08)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
PET-CT scans	£59.84	Gamma (5.98)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
Ultrasound	£12.31	Gamma (1.23)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019

Variable	Value	Distribution and SE for sensitivity analysis	Reference to section in submission	Source
Nuclear medicine studies	£22.33	Gamma (2.23)	B.3.5.3	Andreas et al, 2018; KOL input; NHS Reference costs 2018-2019
CNS metastasis				
One-off radiotherapy	£11,404.29	Gamma (1140.43)	B.3.5.3	NICE TA536; NHS Reference costs 2018-2019
Cycle cost	£386.87	Gamma (38.69)	B.3.5.3	NHS Reference costs 2018-2019; PSSRU 2019
End of life care				
Terminal care	£2,219.80	Gamma (221.98)	B.3.5.3	Brown et al.; NICE TA654; NHS Reference costs 2018-2019; PSSRU 2010 and 2019
Other costs				
EGFR mutation test	£208.98	Gamma (20.89)	B.3.5.5	NICE DG9; PSSRU 2019

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; EGFR, epidermal growth factor receptor; 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 53 summarises the key model assumptions used in the model.

Table 53: Main model assumptions

Parameter/ Model setting	Assumption	Relevant section in submission
Survival outcomes and cure timepoint	The model is largely based on data from an interim analysis of the ADAURA trial, therefore extrapolations of survival outcomes were necessary. However, when extrapolated OS and DFS curves were presented to clinical experts, 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. In addition, the clinicians felt the extrapolations were unrealistic given the unprecedented efficacy of osimertinib demonstrated in the ADAURA trial and the expectation of a functional cure after 5 years DF. To reflect the clinicians' expected clinical outcomes using trial data, parametric distributions were selected and a 5-year cure timepoint was applied, taking into account their expectation of a plateau towards the 5-year mark (disease-free patients are typically discharged and not followed by clinicians after 5 years, and therefore are considered to be functionally cured). Even though the data from ADAURA is based on interim analysis, significant attempt was made to incorporate survival outcomes and functional cure in the model that best reflect current and expected clinical outcomes.	B.3.3
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,[89] which formed the basis of TA654.[90] 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.[18]	B.3.3.5
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,[44] 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).[29]	B.3.4
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.	B.3.4

Parameter/ Model setting	Assumption	Relevant section in submission
	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).[29]	
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. However, it is not possible to accurately predict what proportion of patients wil 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 5 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.	B.3.5.2.1

Abbreviations: DF, disease-free; DM1, 1st line distant metastasis; DM2, 2nd line distant metastasis; HRQoL, health-related quality of life; HSUV, halth 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 54.

[redacted] B.3.5.2.2 [redacted] Osimertinib resulted in [redacted] additional QALYs compared with placebo (active monitoring), and incremental costs of [redacted], resulting in an ICER of £12,849 per QALY.

Table 54: Base-case results per patient

Treatment	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG†	QALYs	Costs (£)	LYG†	QALYs	
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12,849
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 55.

Table 55: 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	NR	27.5	148.6	24.9
OS	[redacted]	[redacted]	175.3	83.1

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 57. A full list of the inputs varied in the PSA, along with the 95% confidence intervals and statistical distribution, is provided in Appendix M.

Table 56: 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

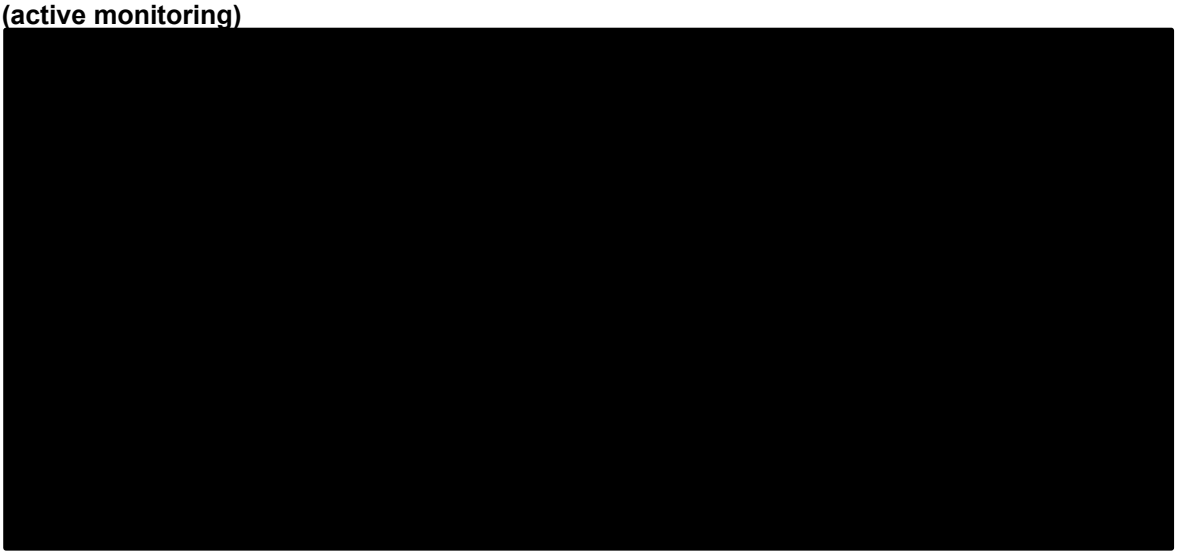
Category	Parameter	PSA distribution
	Disease management costs	Gamma
	Terminal care costs	Gamma
	AE costs	Gamma
	EGFR testing costs	Gamma
	CNS metastasis costs	Gamma

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 41, and illustrates the uncertainty around the incremental costs and QALYs in the model. The tabulated results are presented in Table 57.

Figure 41: 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

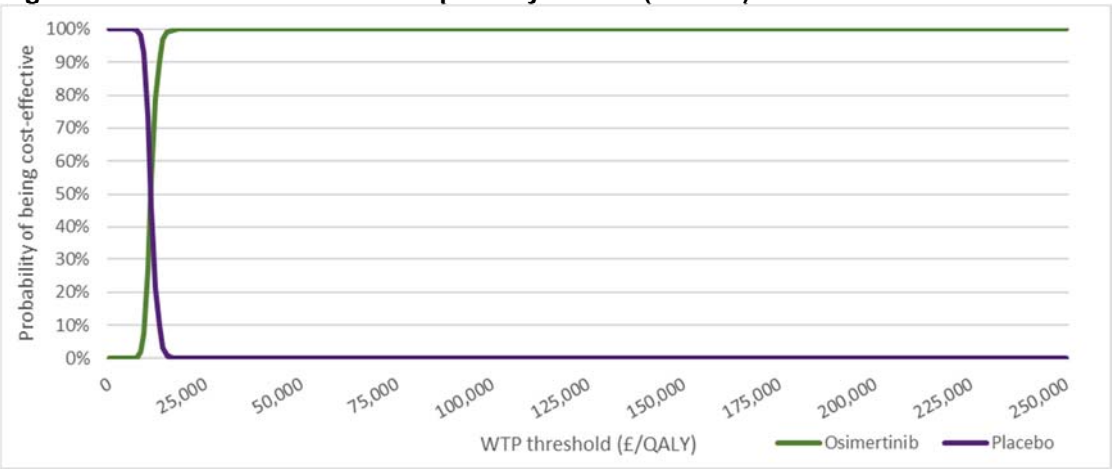
Table 57. Mean PSA results (reference case analysis) per patient

Treatment	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	10,878
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 42.

Figure 42: 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 £10,878 per QALY compared to £12,849 per QALY in the deterministic base case analysis, with osimertinib reaching a 100% probability of cost-effectiveness for thresholds of £18,000 per QALY or greater. This represents a decrease of 15% compared to the base case analysis, indicating that the results of the PSA were broadly consistent with the deterministic results and that the analysis was generally robust with regards to stochastic parameter uncertainty.

B.3.8.2 *Deterministic sensitivity analysis*

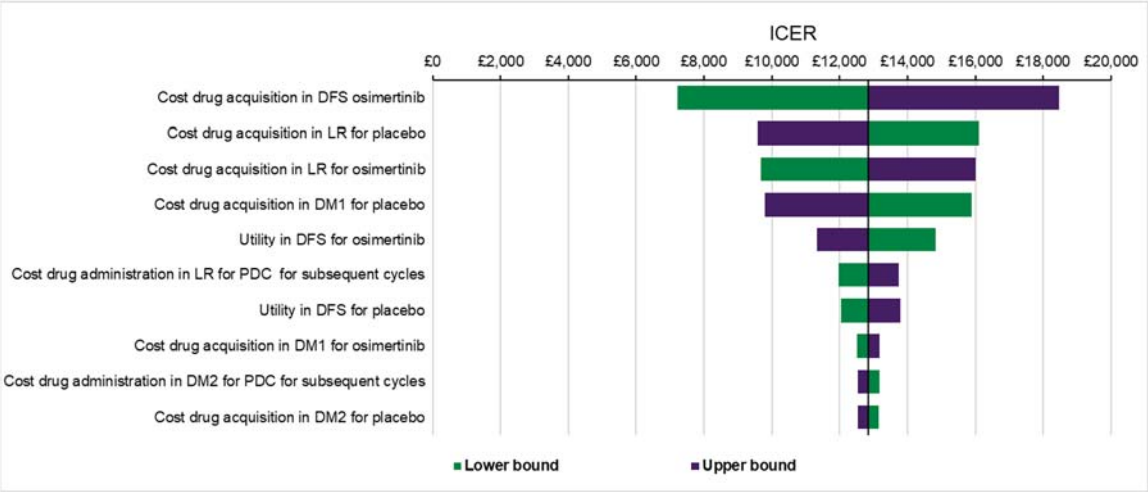
One-way deterministic sensitivity analysis (DSA) was performed to identify key model drivers. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available (e.g. for utilities), or using standard errors estimated 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 M. 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 43, which illustrates the key drivers of the model and their impact on the cost-effectiveness. The 10 parameters which had the largest impact on the ICER, along with their estimated ICERs, are shown in Table 58.

Figure 43: DSA results – tornado diagram



Abbreviations: DFS, disease-free survival; DM, distant metastasis; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; LR, locoregional; PDC, pemetrexed, cisplatin.

Table 58: DSA results – key model drivers

Parameter	Lower bound ICER	Upper bound ICER	Absolute difference
Cost drug acquisition in DF osimertinib	£7,220	£18,478	£11,258
Cost drug acquisition in LRR for placebo (active monitoring)	£16,114	£9,584	£6,530
Cost drug acquisition in LRR for osimertinib	£9,679	£16,019	£6,340
Cost drug acquisition in DM1 for placebo (active monitoring)	£15,901	£9,797	£6,104
Utility in DF for osimertinib	£14,820	£11,341	£3,479
Cost drug administration in LRR for PDC for subsequent cycles	£11,958	£13,740	£1,783
Utility in DF for placebo (active monitoring)	£12,034	£13,783	£1,749
Cost drug acquisition in DM1 for osimertinib	£12,516	£13,182	£665
Cost drug administration in DM2 for PDC for subsequent cycles	£13,173	£12,525	£648
Cost drug acquisition in DM2 for placebo (active monitoring)	£13,162	£12,537	£625

Abbreviations: DF, disease free; ICER, incremental cost-effectiveness ratio; LRR, locoregional recurrence; PDC, pemetrexed, cisplatin.

Treatment cost parameters had the greatest impact on the ICER, the top three being: the drug acquisition cost of osimertinib in DF, the drug acquisition costs in LRR (i.e. the cost of chemoradiotherapy) for both the placebo (active monitoring) and osimertinib arms. However, all of these parameters varied in the DSA resulted in an ICER less than £18,478 per QALY (i.e. highest ICER reached when increasing the cost drug acquisition costs for osimertinib in the DF state).

B.3.8.3 *Scenario analysis*

The following scenario analyses were performed:

- Discount rates 1.5%
- Cure timepoint 4 years
- Cure timepoint 6 years
- Cure percentage 90%
- Cure percentage 100%
- Cure timepoint 4 years with 1-year warmup increasing 50% to 95% cure
- Retreatment timepoint 4 years
- Retreatment timepoint 6 years
- Osimertinib retreatment percentage 40%
- Osimertinib retreatment percentage 60%
- Second-best fit viable survival curves:
    - TP1 (DF to LRR): generalised gamma
    - TP4 (LRR to DM1): loglogistic
    - TP6 (DM1 to DM2): generalised gamma
    - TP8 (DM2 to death): generalised gamma
- HR adjustment to DM1 to DM2 transition probability
- Mean health state utilities from Andreas et al, 2018,[29] (DF=0.72; LRR=0.62; DM1 & DM2=0.67)
- Mean health state utilities from Andreas et al, 2018,[29] for DF and LRR states but with UK-specific mean health state utility for DM1 and DM2 states (DF=0.72; LRR=0.62; DM1 & DM2=0.59)
    - This scenario was conducted to assess a more realistic scenario when the utility from LRR to DM states decrease as expected (and not increase as in the previous scenario)
- EGFR test cost excluded

The results of the scenario analyses are presented in Table 59.

Table 59: 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]	£12,849
Discount rates 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,147
Cure timepoint 4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,616
Cure timepoint 6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,694
Cure percentage 90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,944
Cure percentage 100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,805
Cure timepoint 4 years with 1-year warmup increasing 50% to 95% cure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,502
Retreatment timepoint 4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,573
Retreatment timepoint 6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,597
Osimertinib retreatment percentage 40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,676
Osimertinib retreatment percentage 60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£13,023
Second-best fit viable survival curves: • TP1 (DF to LRR): generalized gamma • TP4 (LRR to DM1): loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,457

Scenario	QALYs			Costs			ICER (£/QALY)
	Osimertinib	Placebo (active monitoring)	Incremental	Osimertinib	Placebo (active monitoring)	Incremental	
• TP6 (DM1 to DM2): generalized gamma • TP8 (DM2 to death): generalized gamma							
HR adjustment to DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,649
Utilities from Andreas et al, 2018 (DF=0.72; LRR=0.62; DM1 & DM2=0.67)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,713
Utilities from Andreas et al, 2018 (DF=0.72; LRR=0.62; DM1 & DM2=0.59)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£14,138
EGFR test cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,821

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

B.3.8.4 *Summary of sensitivity analyses results*

Majority of the scenarios did not increase or decrease the ICER by more than 7%. The scenarios that were most impactful on the results changed the ICER by:

- −29% (to £9,147 per QALY) when the 1.5% discount rates were tested,
- 15% (to £14,713 per QALY) when the utilities were replaced with the following utilities from Andreas et al, 2018: DF=0.72; LRR=0.62; DM1 & DM2=0.67,
- 13% (to £14,457 per QALY) when second best fit viable survival curves were selected,
- 10% (to £14,138 per QALY) when the utilities were replaced with the following utilities from Andreas et al, 2018: DF=0.72; LRR=0.62; DM1 & DM2=0.59.

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, the overall population is the main population of relevance and no subgroup analyses are presented because a consistent treatment effect was observed, and therefore the analysis is based on the full population in line with the anticipated license.

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 techinal design and implementation of the calculations, as well as logic and extreme value testing. Details of the validation process are provided in Appendix N (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).

[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 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 an ICER of £12,849 per QALY gained, compared to a treatment arm including placebo (active monitoring). Furthermore, compared to placebo (active monitoring), the arm including osimertinib also produced considerable clinical and patient benefits, including [redacted] additional life years ([redacted]) and [redacted] additional discounted QALYs ([redacted]) per patient on average.

DSA indicated the model was robust, resulting in ICERs below £19,000 per QALY in all one-way scenarios. Drug acquisition cost for osimertinib in the DF state yielded the largest deviation from the base case, giving ICERs of £7,220 and £18,478 per QALY gained under the upper and lower 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 all runs well under WTP thresholds of £20,000 and £30,000 per QALY gained. Cost-effectiveness acceptability curves demonstrated that the osimertinib arm became the most cost-effective treatment option at a WTP threshold of approximately £11,000 per QALY gained, going on to become 100% cost effective at a threshold of approximately £18,000 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 – £14,713 per QALY gained – occurring when all utilities were replaced with the mean health state utilities from Andreas et al. 2018.[29] Lowering discount rates to 1.5% reduced the ICER to £9,147 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 £12,849 per QALY versus placebo (active monitoring). This ICER is below conventional NICE thresholds of £20,000–£30,000 per QALY and at a WTP threshold of £20,000 per QALY, osimertinib has a 100% probability of being cost-effective.

B.4. References

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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 [ID3835]

Clarification questions

[February 2021]

File name	Version	Contains confidential information	Date
ID3835 Osimertinib Clarification letter company response_V2_[ACIC]	1	Yes	17th March 2021

Notes for company

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Section A: Clarification on effectiveness data

Treatment pathway and licensed indication

A1. Priority question: CS, Section B.1.1. Is it anticipated that the licensed indication set out in the final Summary of Product Characteristics for adjuvant osimertinib will stipulate a maximum treatment duration of 3 years?

Response: The Summary of Product Characteristics (SmPC) is likely to include the following statement within the posology section: [redacted]

A2. CS, Section B.1.3.4., Figure 3, page 25 and Figure 4, page 29. Clinical advisors to the ERG, and the final NICE scope, suggest that some patients would receive adjuvant radiotherapy. Please clarify why this does not appear in CS Figure 3 or Figure 4.

Response: Adjuvant radiotherapy is not included in the treatment algorithm for patients with stage IB–IIA EGFRm NSCLC as it is not deemed standard of care in these patients. Following further engagement with UK clinical experts, clinicians advised that only a very small number of patients would receive adjuvant radiotherapy and therefore is not considered standard practice. This is consistent with the European Society for Medical Oncology (ESMO) guidelines that do not recommend the use of post-operative radiotherapy (PORT) in completely resected early-stage NSCLC. PORT is not considered standard treatment but may be used in selected patients with stage IIIA N2 disease.[1] In addition, the US National Comprehensive Cancer Network (NCCN) 2020 guidelines state that in patients treated with surgery, PORT is not recommended unless there are positive margins or upstaging to N2 disease.[2]

The use of adjuvant radiotherapy is not aligned with the ADAURA trial design; so, together with the insignificant number that receive it in UK clinical practice, it is not considered standard of care and therefore has not been included as an option within the treatment pathway.

A3. CS, Section B.1.3.4., Figure 3, page 25 and Figure 4, page 29. Clinical advisors to the ERG suggest that patients with loco-regional recurrence may receive either single-agent radiotherapy or chemoradiation. Please clarify why single-agent radiotherapy does not appear in CS Figure 3 or Figure 4.

Response: Clinical advisors to the Company reported that the vast majority of patients with stage IB–IIIA EGFRm NSCLC receive chemoradiation when they progress to the loco-regional disease state. Chemoradiation is therefore considered the standard of care in routine clinical practice. The use of single-agent radiotherapy is low and varies across the UK. Upon validating the treatment pathway with clinicians, the Company were advised that less than 18% of patients with stage IB–IIIA EGFRm NSCLC would receive single-agent radiotherapy.

However, to reflect UK practice, the base case analysis has been updated to include single-agent radiotherapy as a treatment for patients with loco-regional recurrence (LRR) (see Appendix A)

A4. Priority question: CS, Section B.1.3.4., Figure 3, page 25 and Figure 4, page 29. Clinical advisors to the ERG, as well as the NICE (2020) Lung Cancer Algorithm for non-squamous NSCLC, suggest that for patients requiring chemotherapy for advanced or metastatic disease (after treatment with osimertinib or other TKIs in CS Figure 3, or instead of osimertinib in CS Figure 4), standard treatment is a four-drug regimen of atezolizumab, bevacizumab, carboplatin and paclitaxel. Please clarify why this four-drug regimen does not appear in CS Figures 3 or 4.

Response: Whilst atezolizumab plus bevacizumab, carboplatin and paclitaxel is recommended as an option for patients with EGFRm-positive NSCLC who have previously received targeted treatment, clinical advisors to the Company stated that the relative proportion of patients receiving treatment with this regimen is small. Clinicians advised that the 4-drug regimen is associated with considerable toxicities and contraindications, resulting in intensive monitoring requirements. In general, clinical advisors stated that a relatively low number of patients are likely to be fit enough to tolerate treatment with the 4-drug regimen, and therefore it does not represent the mainstay treatment in the 2L metastatic NSCLC (mNSCLC) disease setting. In addition, IQVIA prescribing data reported that just 16% of patients received the 4-drug regimen for the 2L treatment of EGFRm-positive mNSCLC in Q4 2020. The limitations of this regimen are also noted in the NICE final appraisal determination (FAD) document for TA584, within which the patient expert highlighted the importance of careful selection of people who would be offered atezolizumab plus bevacizumab, carboplatin and paclitaxel in clinical practice.[3] In addition, the Cancer Drugs Fund (CDF) lead stated that this regimen should only be considered appropriate for patients with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 because of the intensive dosing regimen as atezolizumab and bevacizumab were being added to chemotherapy and the dose of carboplatin would be higher than typically used in clinical practice. As a result, it was concluded that the number of EGFRm-positive patients requiring treatment for 2L

mNSCLC with a performance status of 0 or 1 and considered well enough to tolerate the 4-drug regimen would be considered small.

Whilst the number of patients receiving treatment with the 4-drug regimen is small, an exploratory analysis was conducted which assumed 16% of patients received the atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) regimen as a second line (2L) treatment for patients with advanced or metastatic EGFRm NSCLC was conducted. The ABCP regimen was incorporated within the health economic model in the DM2 health state, implemented using OS data from the IMPower150 trial to model the transition to death, and PFS data to model treatment discontinuation. The impact on the ICER is minimal, with the revised base case ICER decreasing from £11,136 to £10,298 per QALY (see Appendix A, Table 6).

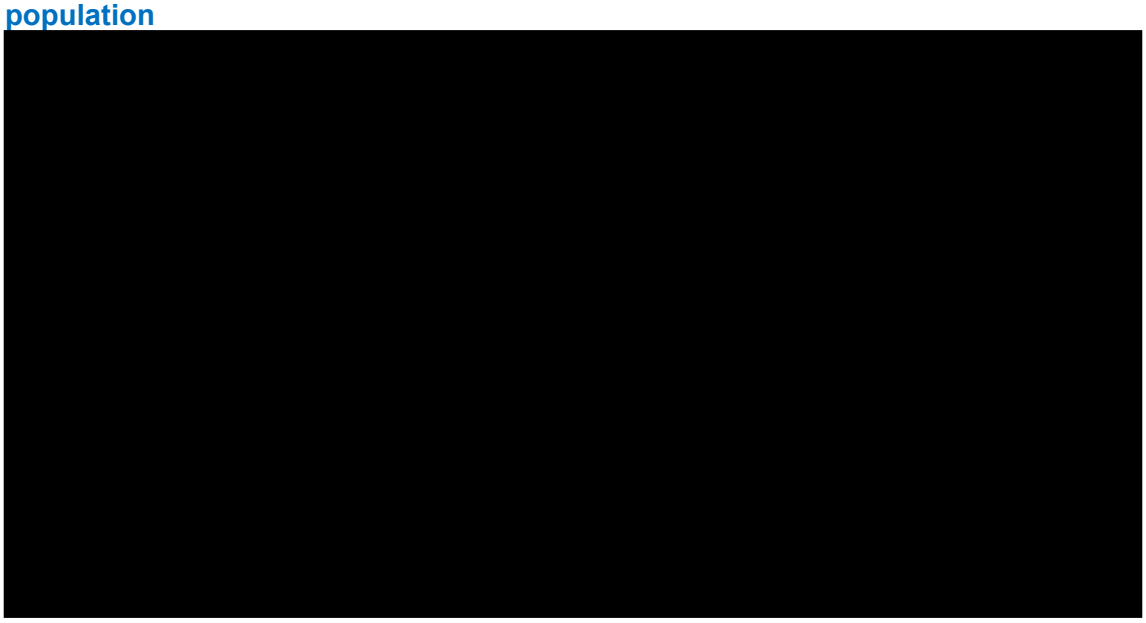
Clinical effectiveness: ADAURA trial

A5. Priority question: CS, Section B.2.3.3., Table 9, page 43. Clinical advisors to the ERG suggest that the ADAURA trial population appears slightly younger, with more females and more never-smokers than would be expected in NHS clinical practice. Please explain whether and how you might expect the treatment effect to differ in an NHS population.

Response: Clinical experts validated the ADAURA population and concluded 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 ADAURA are considered to be reflective of UK clinical practice. The disease-free survival (DFS) benefit observed with osimertinib in the ADAURA trial was consistent across all pre-defined subgroups, providing confidence in the generalisability of the results to patients in the UK.

Figure 1 shows that the DFS hazard ratios (HRs) for sex, age and smoking history all overlap, therefore demonstrating the consistent treatment effect of osimertinib.

Figure 1. Subgroup analysis of DFS in ADAURA – interim analysis in overall population



Abbreviations: DFS, disease-free survival; CI, confidence interval.

The 2020 National Lung Cancer Audit (NLCA; for the 2018 audit period) reports the median age of patients diagnosed with NSCLC as being 73 years, with approximately 53% of these being male.[4] However, whilst it may appear that patients in the ADAURA trial may be slightly younger and may include a greater proportion of females, it is important to consider that these data from the NLCA are reflective of the entire NSCLC population, with 49% diagnosed with stage IV disease, and therefore likely to be older than those who would have been diagnosed with earlier stage disease. Furthermore, clinical experts have advised that patients with EGFR mutations are often younger than those without mutations. Therefore, when considering patients diagnosed with early stage, resectable disease, and those with EGFR mutations, clinicians believed the population in the ADAURA clinical trial was generalisable to those seen in UK clinical practice.

A6. CS, Section B.2.6., page 49-50. The effectiveness results for ADAURA are presented with 99.12% or 99.06% confidence intervals. The ERG understands that this reflects the approach taken to control Type 1 errors when there is multiple testing. Please clarify the calculations used to determine these confidence limits.

Response: The adjusted confidence interval (CI) was computed at the 2-sided 99.06% (primary population: stage II–IIIA) and 99.12% (overall population: stage IB–IIIA) level, considering a 2-sided significance level of 0.0094 and 0.00885, respectively, for the interim analysis, based on the O'Brien and Fleming spending function.[6] Two unplanned interim analyses of DFS were conducted at the time of observing 86 and 156 DFS events in the stage II–IIIA and 109 and 196 DFS events in the overall population. This equated to an information fraction of approximately 0.35 and 0.63, where the final number of events would have been 247 (primary population) and 317 (overall population).

The Lan DeMets approach that approximates the O'Brien and Fleming spending function was used to maintain an overall 2-sided 5% type I error.[7] Using statistical software package EAST®, the following stopping boundaries are obtained and shown below in Table 1.

Table 1: Alpha allocation under Lan-DeMets with O'Brien-Fleming type spending function

Study population	Number of events/information fraction/maturity	Critical value (HR)	2-sided p-value
Overall population (stage IB–IIIA)	196/0.62/29%	0.6886	0.00885
Primary population (stage II–IIIA)	156/0.63/33%	0.6588	0.009384

Abbreviations: HR, hazard ratio.

A7. CS, Section B.2.6.1.3., page 57. In ADAURA, the CS suggests that [redacted] Are there any reasons why this might be?

Response: In ADAURA, health-related quality of life (HRQoL), assessed using SF-36, was collected until disease recurrence, treatment completion (3 years) or

treatment discontinuation; whichever came first. Therefore, the impact of disease recurrence on HRQoL in either treatment arm would not be captured.

In the overall patient population (stage IB–IIIA), HRQoL was overall maintained in both arms. A comparison of mental and physical component summary (MCS and PCS) scores (SF-36) in both treatment arms is shown in Table 2. Scores are shown up to Week 96 to ensure balanced comparison between arms due to earlier disease recurrence in patients receiving placebo.

Table 2: Summary of SF-36 scores – Overall population

Domain/Score	Time point	Osimertinib			Placebo		
		N	Mean	SD	N	Mean	SD
PCS	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCS	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 96	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: MCS, mental component summary; PCS, physical component summary; SD, standard deviation.

Clinically meaningful deteriorations were analysed in the primary study population (stage II–IIA). There was no difference between the arms in the time to confirmed deterioration or death in the mental component of SF-36. No difference in time to treatment deterioration (TTD) of MCS or death was observed between the osimertinib and placebo arms [redacted]

However, given that the comparison was made against patients in the placebo arm, in which treatment-related adverse events (AEs) are not expected, a trend of shorter time to confirmed deterioration or death in the physical component of the SF-36 was observed in the osimertinib arm. It is expected that an active experimental drug is likely to cause more side effects than a non-active (placebo) comparator and given the increased time on treatment on osimertinib, the proportion of patients

experiencing AEs is likely to be higher by virtue of the longer exposure to active treatment.

A post-hoc exploratory analysis, using a mixed model of repeated measures (MMRM), was conducted in the overall patient population (stage IB–IIIA) to analyse changes in SF-36 T-scores from baseline until Week 96.[8] SF-36 scores were calculated using norm-based scoring relative to the general population's[a] mean values, resulting in T-scores. Clinically meaningful changes at the individual (PCS ±3.8 points, MCS ±4.6 points; TTD analyses) and group (PCS ±2 points, MCS ±3 points; MMRM analyses) level were assigned based on pre-specified definitions from the SF-36 user manual (third edition).[9]

In disease-free (DF) patients receiving osimertinib, SF-36 PCS and MCS were maintained from baseline to Week 96, with no clinically meaningful differences observed compared with the placebo arm (Table 3;

[a] SF-36 normative data was calculated based on a 2009 sample of US adults aged ≥18 years, including healthy individuals, and those with chronic conditions

Figure 2).

Table 3: Adjusted mean change in SF-36 PCS and MCS summary T-scores

SF-36 Domain	Mixed model of repeated measures – adjusted mean change from baseline (95% CI)			Definition of clinically meaningful change based on the third edition of the SF-36 scoring manual
	Osimertinib	Placebo	Osimertinib - placebo	
PCS	1.13 (0.54, 1.72)	2.31 (1.70, 2.91)	–1.18 (–2.02, –0.34)	±2
MCS	1.34 (0.60, 2.08)	2.68 (1.92, 3.44)	–1.34 (–2.40, –0.28)	±3

Abbreviations: CI, confidence interval; MCS, mental component summary; PCS, physical component summary.

Figure 2: Adjusted mean change in SF-36 PCS and MCS summary T-scores

†number of patients with data available at each visit; ‡error bars represent SD.
Abbreviations: CI, confidence interval; MCS, mental component summary; PCS, physical component summary; SD, standard deviation.

TTD was defined as time from randomisation to first confirmed clinically important worsening/death. During the DF period, the majority of patients (>80% of patients across both arms) did not experience a clinically meaningful deterioration in PCS or MCS. For those patients who had deterioration, there were no statistically significant differences in TTD of PCS (HR 1.17 [95% CI 0.82, 1.67]) or MCS (HR 0.98 [95% CI 0.70, 1.39]) between osimertinib and placebo.

Figure 3: Time to deterioration of PCS and MCS summary scores

Abbreviations: MCS, mental component summary; PCS, physical component summary.

In conclusion, the post-hoc analysis determined that HRQoL was maintained during adjuvant osimertinib treatment with no clinically meaningful differences versus placebo, despite patients receiving prolonged active treatment.

A8. CS, Section B.2.10.1., page 61. What was the nature of the 1 serious interstitial lung disease (ILD) event in the osimertinib arm of ADAURA, and why was it not classed as severe?

Response: It is important to note that the seriousness and severity of AEs are based on different criteria, so an AE can be serious but not severe and vice versa.

The severity of an AE was graded according to the National Common Terminology Criteria for Adverse Event (CTCAE), version 4.03.[10]

As per the ADAURA statistical analysis plan, a serious adverse event (SAE) was an AE that occurred during any study phase (i.e. run-in, treatment, washout, follow-up), that fulfilled one or more of the following criteria

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Only one ILD event was reported as a SAE. In this case, the patient was hospitalised in case of symptomatic worsening. Hospitalisation therefore resulted in this event being classed as SAE. However, the CTCAE severity grade of the ILD event was grade 2 (moderate) according to criteria (version 4.03).[10] All patients with ILD events, including the one patient who experienced a serious ILD event, were reported to have recovered.

A9. CS, Section B.2.10.1., Table 15. How many Grade 3 or higher AEs (in total, not only potentially related to treatment) occurred in each arm of ADAURA?

Response: AEs that were CTCAE grade 3 or higher occurred in [redacted] in the osimertinib arm, and [redacted] in the placebo arm (Table 4).
Grade ≥3 AEs reported by ≥2 patients in either treatment arm are listed in Table 5; all grade 4 AEs in ADAURA are listed in Table 6.

Table 4: AEs by CTCAE grade ≥3 and 4 in ADAURA by treatment arm

Patients, n (%)	Osimertinib (N=337)	Placebo (N=343)
Patients with AE of CTCAE grade ≥3	[redacted]	[redacted]
Patients with AE of CTCAE grade 4	[redacted]	[redacted]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Table 5: Common CTCAE grade ≥3 AEs in ADAURA reported by ≥2 patients

Patients, n (%)	Osimertinib (N=337)	Placebo (N=343)
[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Table 6: All CTCAE grade 4 AEs in ADAURA

Patients, n	Osimertinib (N=337)	Placebo (N=343)
[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

A10. Priority question. CS, Section B.2.6.1.1., page 52. *P*-values are presented for treatment interaction with stage and mutation type. Please provide *p*-values for all interactions tested.

Response: As per the ADAURA statistical analysis plan, 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 model including treatment, covariates for race, stage, mutation status and region, and all covariate-by-treatment interaction terms, with one that excluded the interaction terms. Once the global interaction test was found to be statistically significant, an attempt was made to determine the cause and type of interaction. This involved

using a stepwise backwards selection approach on the fully saturated model, whereby (using a 10% significance level threshold) the least significant interaction terms were removed one-by-one until all interaction terms remaining were significant.

The backwards stepwise selection approach removed all predictors with the exception of stage and mutation type (Ex19del vs L858R) in the overall population (stage IB–IIIA), and mutation type in the primary population (stage II–IIIA), which were found to be significant at the 10% significance level. As these were the only significant interactions in the model, the p-values denoting strength of the significance and whether these involved directional and/or magnitude changes (quantitative/qualitative) have already been presented (CS, Section B.2.6.1.1., page 52). The p-values for the remaining interactions were tested, however these were found to be non-significant (p>0.1) and removed in the process of reaching the final model, therefore the p-values for these interactions have not been presented.

A11. CS, Section B.2.6.2.1., Figures 7,8, 10 and 11, pages 49-56. Please provide versions of KM plots which have confidence intervals at representative timepoints.

Response: The Kaplan-Meier (KM) plots in the overall and primary population for DFS and overall survival (OS) with 95% CI are shown in

Figure 4 to Figure 7 below.

Figure 4: KM plot of DFS in ADAURA – interim analysis in overall population

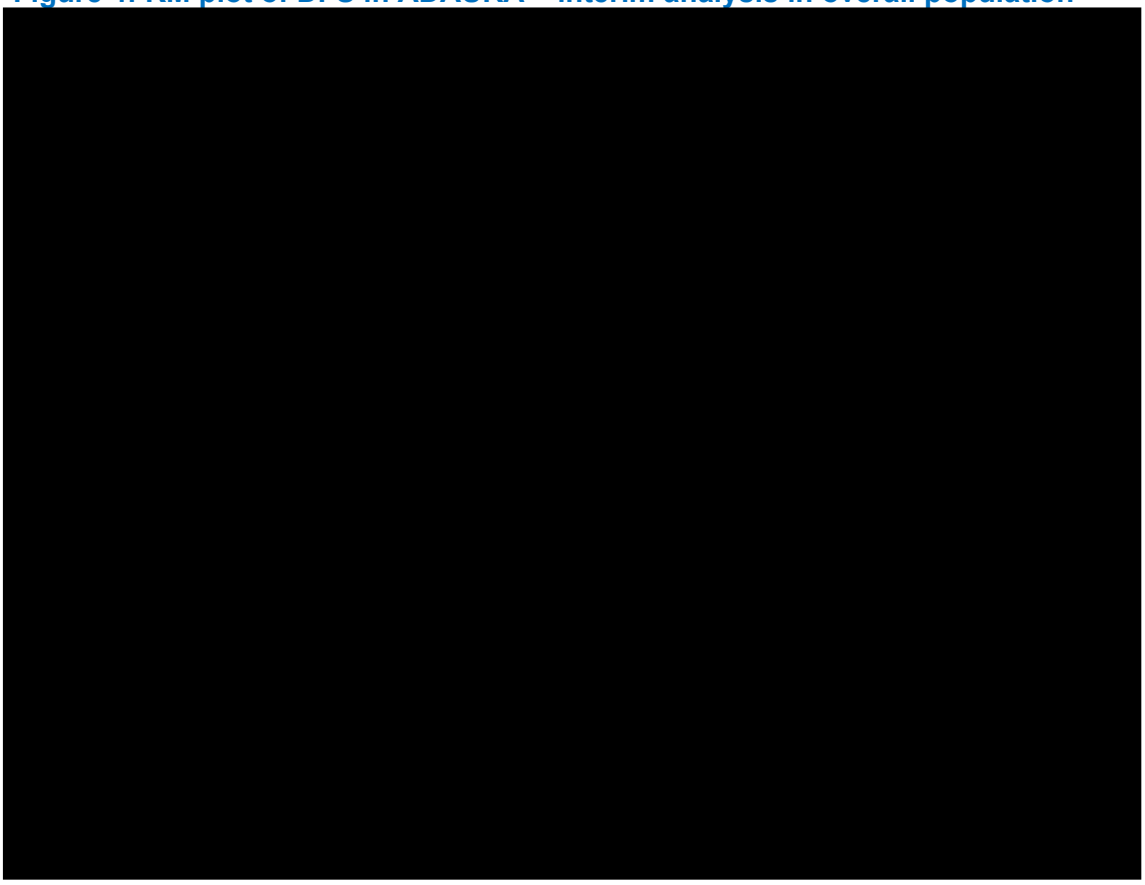


Figure 5: KM plot of DFS in ADAURA – interim analysis in stage II–IIIA population

Figure 6: KM plot of OS in ADAURA – interim analysis in overall population

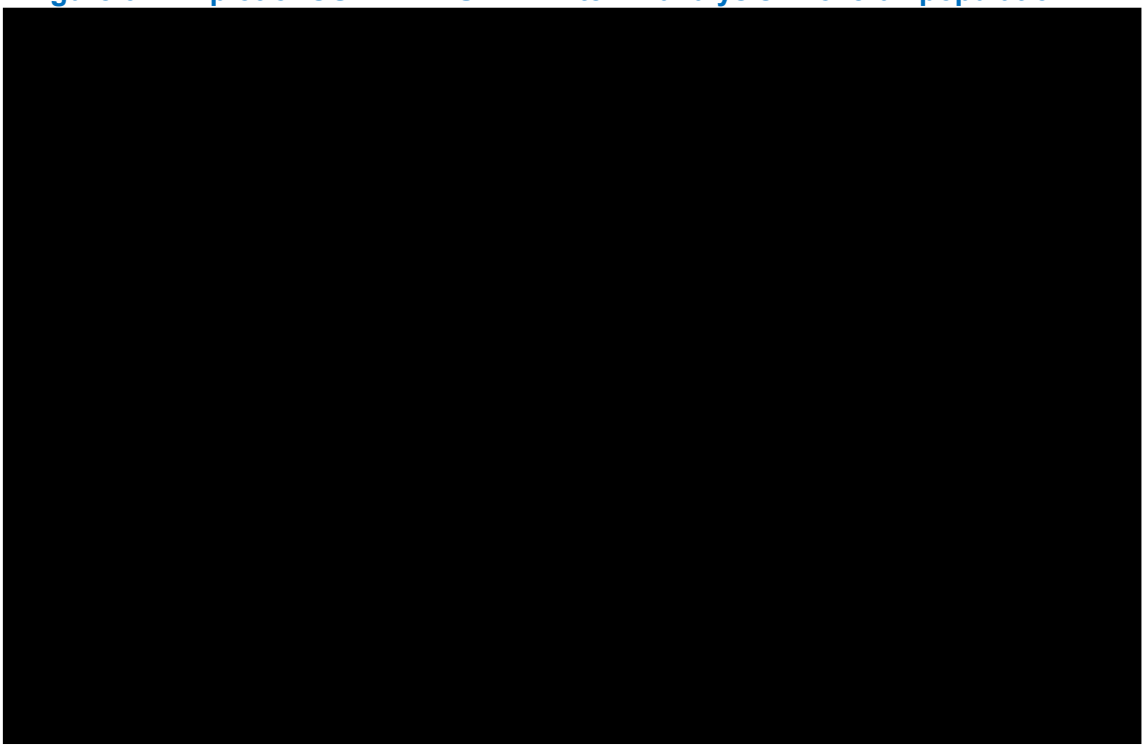


Figure 7: KM plot of OS in ADAURA – interim analysis in stage II–IIIA population

A12. Priority question. CS, Section B.2.6.1.1., page 53. Please provide *p*-values for differences in proportions having recurrence by 36 months.

Response: In the overall population, [redacted]. Statistical tests were not undertaken to compare proportions of recurrences that occurred within 36 months between treatment arms.

The preferred analysis for comparison of recurrence between the treatment groups is a time-to-event analysis such as that using a KM analysis method, where a patients' survival time is taken into account in addition to their event status, the latter of which is only factored in a binary analysis where information on the survival time is discarded. The proportions were presented to demonstrate that, in addition to the higher probability of patients experiencing disease recurrence in the placebo arm (CS, Section B.2.6.1.1.,Table 13), a larger proportion had done so within the maximum time on treatment. As such, the 5.4% of recurrences on osimertinib after 36 months, were likely to have occurred once exposure to osimertinib had ceased.

The results of the time-to-event KM analysis, accounting for patient censoring and survival time, demonstrated landmark estimates at 36 months of [redacted] in the overall population, with no overlap in 95% CIs between these two groups. Although this analysis does not attribute a time element to when the recurrences occurred, it demonstrates that a significantly larger proportion of patients were recurrence-free at 36 months in the osimertinib arm compared with the placebo arm.

A13. Priority question. CS, Section B.2.6.1.2., page 54. Please provide the HR and 95% CI for overall survival in the overall population.

Response: As per the study statistical analysis plan, OS was initially formally tested in the primary population (stage II–IIIA) patients at the current data cut-off, with the overall population only tested should statistical significance be reached in the primary population. At the data cut-off, 25 deaths had occurred in stage II–IIIA patients (5.3% maturity of data), comprising 8 patients (3.4%) in the osimertinib arm and 17 patients (7.2%) in the placebo arm. The HR was 0.40 (99.98% CI: 0.09, 1.83; p=0.0244), which did not reach statistical significance (p-value <0.0002 required).

[redacted] In this population, 9 patients (2.7%) in the osimertinib arm and 20 patients (5.8%) in the placebo arm had experienced an OS event at the current data cut-off [redacted]

Table 7: OS analysis – Overall population

n (%)	Osimertinib	Placebo
N	[redacted]	[redacted]
Number (%) of patients with events[a]	[redacted]	[redacted]
Hazard ratio (95% CI)[b]	[redacted]	
99.98% CI[c]	[redacted]	
2-sided p-value	[redacted]	

[a] OS 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] The 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. A HR <1 favours osimertinib. The HR and CI are obtained directly from the U and Vstatistics (Berry et al 1991; Selke and Siegmund 1983).
[c] The adjusted CI is computed at the 2-sided 99.98% level, considering a 2-sided significance level of 0.0002 for the interim analysis, based on the Haybittle-Peto spending function.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
Sources: ADAURA CSR.[11]

A14. CS, Section 2.10.1, page 60. Please provide *p*-values for differences in AEs between groups.

Response: Statistical comparisons of AE data were not presented as the ADAURA study was not powered to detect any significant differences between the two groups with respect to AEs encountered. In addition, this analysis was not pre-specified in the statistical analysis plan.

Given the number of AEs listed in the study, formal statistical comparisons of each AE would result in a large number of tests being carried out with the risk of chance findings owing to multiplicity of testing, increasing with each AE tested. There is also a likelihood that patients who experience one type of AE are more likely to experience others, inducing a correlation which independent testing ignores, and therefore may mis-represent any comparisons drawn here. It is also expected that an active drug is likely to cause more side effects than a non-active (placebo) comparator and, given the increased time on treatment on osimertinib, the proportion

of patients experiencing AEs is likely to be higher due to the longer exposure to active treatment.

The total median exposure to osimertinib (22.5 months) was longer than in the placebo arm (18.7 months), consistent with the longer median DFS in the osimertinib arm. As expected, the frequency and severity of AEs was higher in the osimertinib arm than in the placebo arm. The only AEs reported with at least a 10% greater incidence in the osimertinib arm than in the placebo arm were diarrhoea, paronychia, dry skin, pruritus and stomatitis, which are all well-characterised adverse reactions associated with EGFR-TKI treatment.[12] The majority of AEs were non-serious, and mild or moderate in severity.

Overall, the ADAURA safety data for osimertinib was consistent with the safety profile of osimertinib treatment observed in previous NSCLC trials and was deemed sufficient to support long-term dosing in the adjuvant setting.[12, 13]

Section B: Clarification on cost-effectiveness data

Model structure

B1. CS, Section B.3.2.2., pages 72-77. The model structure suggests that all patients who reach DM1 receive active first-line therapy and all patients who reach DM2 receive active second-line therapy. Please comment on the plausibility of this assumption.

Response: UK clinical advice received by the Company confirmed that patients with EGFR mutation positive mNSCLC are generally younger and fitter than patients without EGFR mutations in UK clinical practice. As a result, the Company was advised that, in general, almost all (>90%) EGFRm mNSCLC patients who are eligible to receive first line (1L) therapy go on to receive active treatment. This is also driven by the availability of targeted treatment options, such as osimertinib, in the 1L setting, and therefore provides a strong clinical rationale for treating patients with EGFR mutations. In addition, clinical advisors stated that a majority of EGFRm positive patients (approximately 75%) also go on to receive 2L treatment. In addition, additional analyses from the ADAURA clinical trial demonstrates that of the [redacted] patients who experienced disease recurrence, [redacted] patient was classed as

having a performance status of 2, with the remaining [redacted] patients having a performance status of 0 or 1. This confirms the conclusions made by the clinical experts in that the majority of patients are considered fit enough to tolerate further treatment at the point of disease recurrence. However, the clinical advisors did note that some patients may have poorer ECOG performance status or have brain metastases and may therefore receive palliative care.

Despite the majority of patients receiving active 1L and 2L treatment in UK clinical practice, we have presented a scenario analyses to explore the impact on the ICER where a proportion of patients are assumed to not receive active treatment. However, due to the unethical nature of not providing active treatment to patients with 1L or 2L mNSCLC in a clinical trial setting, there is a paucity of data to inform the relative transition probabilities in the economic model for patients who are assumed to not receive treatment. Therefore, in line with the approach adopted in TA584, we have altered the cost inputs whereby 10% and 25% of patients in the 1L and 2L setting, respectively, are assumed to not receive active treatment. In this scenario the updated base case ICER increases from £11,136 to £12,932 (Appendix A, Table 6).

B2. Priority question. CS, Section B.3.2.2., pages 72-77. The economic model assumes that all patients in the comparator group receive osimertinib as a first-line treatment for distant metastases. However, the ERG understands that some patients currently receive afatinib, dacomitinib, erlotinib, or gefitinib as first-line treatment for metastatic disease, and some receive a 4-drug regimen of atezolizumab, bevacizumab, carboplatin and paclitaxel as second-line treatment for metastatic disease (note: some of these treatments appear in CS Figure 3). Please clarify why none of these other treatments have been included as current treatments in the economic model.

Response: With regards to the use of atezolizumab, bevacizumab, carboplatin and paclitaxel as 2L treatment for metastatic disease, please refer to our answer in response to question A4.

With regards to the other tyrosine kinase inhibitors (TKIs):

Since the positive NICE recommendation for osimertinib in the 1L metastatic setting in September 2020 (TA654),[14] clinical advisors unanimously advised that osimertinib represents the mainstay 1L treatment option for EGFRm positive mNSCLC patients in England. Clinicians advised that osimertinib is preferred over earlier generation TKIs due to the improved response levels and survival, extracranial efficacy, and the prevention of EGFR T790m resistance mutations provided by osimertinib. Therefore, clinicians advised that it was vital for patients to receive the most efficacious treatment option which prevents the onset of the T790m resistance mechanism observed with other TKIs, and therefore there was no clinical rationale for choosing an alternative TKI since the positive recommendation by NICE. National prescribing data provided by IQVIA shows that, since publication of the positive guidance for osimertinib, the uptake of osimertinib use in the 1L metastatic setting has increased significantly; accounting for [redacted] of all TKI prescribing across Q4 2020 compared with just [redacted] in Q1 2020, and is expected to significantly increase with the availability of more recent data following the recommendation in September 2020 Therefore, any newly diagnosed incident patients are expected to receive 1L osimertinib in the mNSCLC disease setting. Despite this, the Company acknowledge that there are a small number of existing patients receiving treatment with other TKIs. An exploratory analysis has therefore been considered, based on Q4 2020 national prescribing data, to include the following TKI mix in the 1L metastatic setting in the placebo arm. However, this analysis is inconsistent with the advice received by practicing clinicians and should therefore should be considered exploratory and does not form the base case.

Exploratory analysis including other EGFR-TKIs in DM1

Placebo arm

In the DM1 health state, the proportion of patients receiving EGFR-TKIs based on Q4 national prescribing data: osimertinib, [redacted]. Given the clinician feedback that osimertinib is now the mainstay treatment option for 1L metastatic NSCLC, this was a highly conservative assumption.

Data from the comparator arm of the FLAURA trial (standard of care EGFR-TKIs, erlotinib/gefitinib) was used to inform the efficacy of EGFR-TKIs.

The inclusion of 1st and 2nd generation EGFR-TKIs in the DM1 health state in the placebo arm affected the subsequent treatments received by patients in DM2. Clinical literature has demonstrated that a proportion of patients receiving 1st or 2nd generation TKIs will test positive for T790M resistance mutation and are therefore eligible for osimertinib in the 2L metastatic setting. Osimertinib was therefore included in the treatment mix in DM2, with [redacted] of patients receiving EGFR-TKI in DM1 assumed to receive osimertinib. The proportion of patients receiving osimertinib for T790M mutation-positive NSCLC was derived from IQVIA prescribing data. In line with the base case, the remainder of patients were assumed to receive PDC.

Osimertinib arm

The treatment mix in the DM1 health state was consistent with the base case analysis (CS, Section B.3.2.3, Figure 15). Osimertinib-treated patients received PDC in DM2. Patients who received PDC in DM1 progressed to receive single agent chemotherapy (docetaxel) in DM2, in line with the base case analysis.

The treatment mix applied in this exploratory analysis is summarised in Table 8.

Table 8: TKI exploratory analysis – DM treatment mix

Health state	Osimertinib arm		Placebo arm				
DM1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DM2	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: PDC, pemetrexed plus cisplatin.

The ICER for this exploratory cost-effectiveness analysis is £19,090 (Appendix A, Table 6).

B3. Priority question. CS, Section B.3.2.2., pages 72-77. Please clarify why the model does not include the use of a 4-drug regimen of atezolizumab, bevacizumab,

carboplatin and paclitaxel as a first-line treatment for metastases following relapse on adjuvant osimertinib (for those patients who are not re-treated with osimertinib).

Response: Atezolizumab plus bevacizumab, carboplatin and paclitaxel was recommended by NICE (TA584) in June 2019 as an option for metastatic NSCLC in adults when targeted therapy for EGFR-positive or ALK-positive NSCLC has failed,[15] and therefore is recommended as a 2L treatment option within the metastatic disease setting. The pivotal clinical trial which underpinned this recommendation came from was the IMpower150 study, where the only data to inform the efficacy for decision making for EGFR-positive mNSCLC patients was in those who had previously received 1L TKI treatment for mNSCLC. The NICE recommendation was made within this context, and therefore this regimen does not have a recommendation for use as a 1L treatment option in patients with EGFRm-positive NSCLC who may have previously received treatment with a TKI as adjuvant therapy for early stage (stage IB–IIIA) NSCLC.

In addition, the licence for atezolizumab states that '*in patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies'* and refers to section 5.1, within which the IMpower150 trial is referenced. In particular, section 5.1 states that *'the ITT population, including patients with EGFR mutations or ALK rearrangements who should have been previously treated with tyrosine kinase inhibitors'*.[16] This is stated within the context of the mNSCLC setting. Therefore, it would appear that atezolizumab plus bevacizumab, carboplatin and paclitaxel does not have a licence for use as a 1L treatment in patients with EGFRm positive mNSCLC. As a result of the above, this regimen has not been included as a 1L option within the pathway following the treatment with osimertinib as adjuvant therapy in stage IB−IIIA EGFRm-positive NSCLC patients.

B4. Priority question. CS, Section B.3.3.3.1, page 79. Please clarify the precise source of the 5-year timepoint at which cure is assumed and the proportion of patients who are assumed to be cured (95%). Were these values suggested by the

company's clinical advisors or by the company? If it was the latter scenario, did the clinical advisors agree with this assumption?

Response: The 5-year cure timepoint applied in the base case analysis was sourced from the interviews conducted with six UK clinical experts. During the interviews, clinicians stated that patients with completely resected, early-stage NSCLC are typically discharged from clinical care after 5 years if they have not experienced disease recurrence. Most clinicians agreed that patients who are DF at 5 years would have a very low risk of recurrence, and that their survival would be similar to that of the general population. Most clinicians agreed that these patients can be considered functionally 'cured'.

As discussed in CS, Section B.3.3.3, Page 81, long-term external clinical trial data in patients with stage IB–IIIA, completely-resected NSCLC (ANITA study) indicates that at around 48–60 months, regardless of treatment arm, a proportion of patients are no longer at risk of disease recurrence, thus providing further support for a functional cure in this patient population.[17]

The assumption that 95% of patients would be cured if they remained DF at 5 years was a company assumption and is consistent with the preferred approach described in NICE technology appraisals in adjuvant, early-stage cancer (TA569, TA642). In both appraisals, the ERG and the appraisal committee agreed that the maximum proportion of patients to be 'cured' at the final timepoint (i.e. no longer at risk of disease recurrence) should be set to 95% and that it was clinically implausible to assume 100% of patients could be 'cured'.

It is necessary to note that despite the strong clinical rationale for cure in this patient population, based on the overwhelming efficacy of osimertinib observed in ADAURA and clinical expert opinion, the immaturity of ADAURA DFS data means that there is some uncertainty around the specifications of the cure assumption. However, not including a cure assumption would have been clinically unrealistic as interviewed clinicians stated that the extrapolated ADAURA DFS curves likely overestimate the long-term rate of disease recurrence and are therefore overly pessimistic for an early-stage, completely resected population.

Nonetheless, it was necessary to explore the uncertainty around the cure assumption by conducting multiple scenario analyses. Scenario analyses presented in CS, Section B.3.8.3, explored applying different cure timepoints, varying the percentage of patients cured, and applying a more continuous flow in the percentage of patients cured by using an interim warm up period of 1 year before 5 years, when 95% of patients are assumed to be cured. Osimertinib remained cost-effective across all scenario analyses.

To further address the uncertainty around the specifications of the cure assumption, scenario analyses have been conducted based on the updated economic model and base case analysis (Appendix A, Table 6).

The scenario analyses below explore the impact of a different cure timepoint for the osimertinib arm (6 years) and a lowered maximum cure rate (85%). Additionally, in the osimertinib arm, the impact of a gradual increase in cure rate from 0% at Year 5 to 95% at Year 10 was also explored.

Table 9: Scenario analyses on the cure assumption

Osimertinib: cure timepoint	Placebo: cure timepoint	Osimertinib and placebo: Maximum cure	ICER (/QALY gained)
5 years	5 years	95%	£11,136
6 years	5 years	95%	£14,958
5 years	5 years	85%	£11,703
6 years	5 years	85%	£15,123
Cure proportion linearly increases from Year 5 to reach a maximum of 95% at Year 10	5 years	95%	£18,822

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

B5. Priority question. CS, Section B.3.5.2.1., page 123. Please clarify the precise source of the assumption that 50% of patients treated with adjuvant osimertinib who later develop distant metastases will go on to be re-treated with osimertinib after 5-years. Was this value suggested by the company's clinical advisors or by the

company? If it was the latter scenario, did the clinical advisors agree with this assumption?

Response: Having an innovative targeted therapy, such as osimertinib, in the adjuvant setting represents a considerable step change in the treatment pathway. Due to the innovative nature of osimertinib, the proportion of patients that would receive osimertinib re-treatment in the metastatic setting is currently uncertain. In the absence of data, the Company ratified the assumption of osimertinib re-treatment with UK clinicians. The clinicians unanimously agreed that should a patient successfully complete 3 years of treatment with osimertinib in the adjuvant setting but relapse after a DF period of at least 1 year, then there is no clear clinical rationale as to why they would not consider re-treatment. However, clinicians stated that it would be unlikely that all patients would be re-treated with TKIs therefore the proportion of patients re-treated with osimertinib is likely to vary across the UK. Following the 1L treatment with osimertinib for the treatment of EGFRm positive mNSCLC patients, data from the FLAURA study demonstrated that of those that went on to receive subsequent therapy, just 28.6% received subsequent treatment with a TKI.[b] Therefore, in the absence of other data, the Company therefore deem the assumption that 50% of patients treated with adjuvant osimertinib who later develop distant metastases will go on to be re-treated with osimertinib after 5-years to be . Scenario analyses were presented for 40% and 60% retreatment with osimertinib in the CS (Section B.3.8.3, Page 155). While the cost-effectiveness of osimertinib reduces with an increase in the proportion of patients being re-treated, it remains within the cost-effectiveness threshold across the range of re-treatment percentages.

Evidence used to inform the model

B6. CS, Section B.3.2.2., page 74. The inclusion criteria for the FLAURA study required patients to have a WHO performance status of 0 or 1. Please comment on

[b] Data obtained from Ramalingam SS et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med. 2020 Jan 2;382(1):41-50. doi: 10.1056/NEJMoa1913662. Epub 2019 Nov 21. PMID: 31751012.

the extent to which the model reflects outcomes for relapsed patients with a lower performance status.

Response: It is necessary to note that patients who relapse following complete surgical resection for early-stage NSCLC are distinct from patients who enter the healthcare system with untreated, locally-advanced or metastatic NSCLC. In the absence of long-term clinical data, the performance status and comorbidities of patients who have relapsed and developed distant metastases is yet to be determined. However, since these patients have already received clinical care for early-stage disease and will be routinely monitored for disease recurrence, it is likely that disease recurrence or relapse in these patients will be identified more quickly than in those who are undiagnosed.

While the inclusion criteria for FLAURA limited the patient population to those with a WHO performance status of 0 or 1, NICE issued a positive recommendation for osimertinib in untreated locally advanced or metastatic EGFRm NSCLC in September 2020 (TA654) and therefore inherently accepts the trial population to be generalisable to those observed in UK clinical practice.[14] This recommendation was irrespective of performance status. Since its recommendation, osimertinib has become the standard of care for this patient population in England.

Despite the immaturity of the data, initial analyses from ADAURA indicate that the majority of patients who discontinued treatment at the point of disease recurrence continued to have a WHO performance status of 0 or 1 ([redacted]). Furthermore, additional analyses from the ADAURA clinical trial demonstrates that of the [redacted] patients who experienced disease recurrence, [redacted] patient was classed as having a performance status of 2, with the remaining [redacted] patients having a performance status of 0 or 1.

Furthermore, real-world evidence suggests that the majority of patients with locally advanced or metastatic NSCLC have a performance status of 0 or 1. During the NICE process for TA654,[14] the Company submitted SACT data that indicated that only 25% of locally advanced or metastatic NSCLC patients had a performance status of 2 or more. Clinical experts have also stated that the majority of patients with metastatic EGFRm-positive NSCLC have a performance status of 0 or 1. This has

been further confirmed following additional clinical engagement where advisors stated that patients with EGFR mutations are generally younger and fitter than patients without EGFR mutations, and are therefore more likely to have a good performance status.

B7. Priority question. CS, Section B.3.2.2., page 74. The model assumes that outcomes for chemotherapy for metastases are equivalent to those from the control arm of the FLAURA trial (gefitinib/erlotinib). However, these treatments are associated with better PFS than chemotherapy. Please comment on the likely bias arising from this assumption and clarify why the HR from the network meta-analysis cited in the CS was not included in the base case model.

Response: To account for the potential differences in efficacy associated with standard of care EGFR-TKI in the FLAURA study compared with chemotherapy in the distant metastasis (DM) health states, a HR adjustment to the DM1 to DM2 transition probability was included in a scenario analysis (see 'HR adjustment to DM1' in section B.3.8.3). Overall survival remains unaffected in this scenario analysis as the network meta-analysis indicated that first-generation EGFR-TKIs and chemotherapy had similar OS. It was not included in the base case analysis as most of the studies used in the network meta-analysis (NMA) to estimate HRs comparing gefitinib to chemotherapy were considered to have relatively heterogenous patient populations (e.g. in terms of age, ethnicity, proportion male), including when compared to the FLAURA trial. Assuming equivalent clinical outcomes may not be conservative; however, as the resultant ICER under this scenario is £12,649 per QALY versus £12,849 per QALY in the base case analysis, the Company took a conservative approach as its base case, as the HR adjustment decreased the ICER. This decrease in the ICER when HR adjustment is applied is mainly due to the reduced time patients spend in the DM state. However, we agree that it is unlikely that the outcomes observed from first/second-generation TKIs is likely to differ to that observed in patients receiving treatment with chemotherapy. Therefore, the HR from the NMA has now been included as part of the Company's updated base case presented in Appendix A.

B8. Priority question. CS, Section B.3.2.2., page 74. The model assumes that the effectiveness of osimertinib for the treatment of metastatic disease is the same

irrespective of whether the patient has previously received osimertinib in the adjuvant setting. Please comment on the plausibility of this assumption and provide any relevant evidence available to support it.

Response: Due to the innovative nature and the fact that osimertinib in the adjuvant setting represents a step change in the treatment pathway for patients with stage IB−IIIA EGFRm NSCLC, there are currently no randomised controlled trial (RCT) data demonstrating the effectiveness of osimertinib re-treatment in the metastatic setting. In the absence of data, the Company have extensively validated with UK clinicians the assumption that the effectiveness of osimertinib for the treatment of metastatic disease is the same irrespective of whether the patient has previously received osimertinib in the adjuvant setting. Clinicians unanimously agreed that should a patient successfully complete 3 years of treatment with osimertinib in the adjuvant setting but subsequently relapse after a DF period of at least 6 months then there is no clear clinical rationale as to why the effectiveness of osimertinib should differ when used in the metastatic setting. Clinicians advised that if a patients has completed 3 years of treatment with osimertinib in the adjuvant setting, then it was likely that patients had not developed TKI-resistant mechanisms, and as a result, further treatment with osimertinib with in the 1L mNSCLC disease setting was unlikely to result in a reduced efficacy profile.

B9. CS, Section B.3.5.2.1, page 123, Figure 40. Please add a “Number at risk” table to Figure 40 (“Time to treatment discontinuation from ADAURA”).

Response: The time to treatment discontinuation KM plot including number of patients at risk is provided in Figure 8.

Figure 8: Time to treatment discontinuation from ADAURA

Parametric survival modelling, including competing risk adjustments and cure assumptions

B10. Priority question. CS, Section B.3.3, pages 77-105. Please comment on how information regarding the nature of the hazard for each event was used to inform the selection of parametric survival models. Was an assessment undertaken to check whether the underlying assumptions made by each survival distribution are consistent with what is believed about the nature of the hazard for each specific event?

Response: The parametric distributions for the individual transitions in the economic model were initially assessed for goodness of fit, determined by the Akaike information criterion (AIC) and Bayesian Information Criterion (BIC). The goodness of fit was also assessed by calculating the mean squared error (MSE) for every possible combination of the parametric distribution in TP1 (DF to LRR) and TP2 (DF to 1L DM), based upon the difference between the aggregated DFS curve and the ADAURA DFS KM curve. The MSE was used to evaluate the goodness of fit of the

long-term extrapolations versus the KM. The same method was conducted for OS. The combination of distributions for the different transitions resulting in the smallest MSE (DFS+OS) were in line with the distributions selected based upon AIC/BIC.

In addition to evaluating how well the parametric distributions fit the observed data from the ADAURA study, the survival curves applied to individual transitions were also visually assessed for clinical plausibility, as recommended by Williams et al. 2017.[18] In the absence of external long-term clinical data to inform the clinical plausibility of the events captured in the model, UK clinical expert opinion was sought to validate the long-term extrapolations of aggregated OS and DFS. A real-world evidence study described in CS, Section B.3.3.6 (Page 110) was also utilised to validate aggregated DFS estimates in the model. Based on the clinical expert's feedback and the external study, the parametric distributions for each of the individual transitions were selected based on their clinical plausibility alongside their goodness of fit to the observed data.

B11. CS, Section B.3.3.3.2, page 87. For TP1 and TP2 (in the DF state), model selection includes consideration of goodness of fit and plausibility of the long-term extrapolation. Some parametric models were excluded because the long-term extrapolations *"were incompatible with the underlying functional cure assumption."* Given that the model includes a fixed cure timepoint of 5 years for 95% of patients, why was clinical plausibility of the models (without cure) considered relevant for model selection in these cases?

Response: Despite the fixed cure timepoint applied in 95% of the patients who are DF at 5 years, the long-term extrapolations of the DF health state are still relevant for the remainder of patients in this health state. Therefore, the long-term extrapolations (without cure) were validated for clinical plausibility for this patient population.

B12. CS, Section B.3.3.4.1., page 93. Please clarify the nature of the external clinical data mentioned in the final paragraph of this section in relation to goodness of fit for TP4.

Response: The Company acknowledge that the mention of external clinical data in this sentence was an error. The clinical plausibility of TP4 was validated by clinical

expert opinion only, as there is no external data that explicitly captures time from LRR to DM in this patient population.

B13. CS, Section B.3.3.5.1., text on page 98 (with reference to Figure 29 on page 99). What were the criteria for deciding that the log-logistic and log-normal extrapolations appear optimistic?

Response: The clinical plausibility of the extrapolations was validated by UK clinicians consulted in interviews. The log-logistic and log-normal parametric distributions were deemed to overfit the tail of the standard of care (SoC) EGFR-TKI arm from the FLAURA trial. However, given the maturity of data from this study, the choice of the parametric distribution does not significantly affect the ICER (CS, Section B.3.8.3).

B14. CS, Section B.3.3.1, pages 77-79. The CS refers to the use of multistate models in the economic model. Did this involve fitting multistate models using the approach and code reported by Williams et al, or is this only referring to the generation of time-to-event data for each endpoint, censoring for the event not of interest, and applying the competing risks adjustment described on page 79 of the CS?

Response: The R code provided in Williams et al, 2017, for a multistate model was used to generate the individual patient level data (IPD) for the three transitions from ADAURA (TP1, TP2, TP3) and FLAURA (TP6, TP7, TP8) for the health economic model.[18] Subsequently, similar to the approach of Williams et al, standard parametric curves were fitted on the individual transitions from each study. The economic model was programmed in MS Excel to maintain transparency throughout the NICE process. As such the parametric distributions fitted in R to each of the individual transitions were implemented in MS Excel. Williams et al developed a fully R-based model that deals with time continuously and considers the Aalen-Johansen estimator for competing risks (e.g. DF-> Death, DF-> DM1, DF-> LR). In MS Excel, time is modelled through discrete time cycles. As such, the competing risks in the model were dealt with by using the exponential distribution to estimate transition probabilities (CS, B.3.3.2, Page 79). To validate the predictions generated, the

Excel-based health state occupancy was compared with R-based model health state occupancy. The results of each model were found to be highly consistent.

B15. Model, worksheets "TP Matrix Comp0" columns U to AF and "TP Matrix Comp1" columns R to AC. These columns include calculations which are intended to adjust for competing risks:

a) Please comment on why the unadjusted transition probabilities are being treated as rates. For example, the underlined section of the following equation =IFERROR(J12/SUM(J12,K12,L12)*(1-EXP(-SUM(J12,K12,L12))),0)

b) With respect to the adjustment of the LRR risks (TP4 and TP5), given that the competing risk of death (TP5) is zero in the calculation, why does this adjustment have any effect on TP4? Is this a consequence of erroneously mixing rates and probabilities?

Response: As described in response to B14, the economic model was programmed in MS Excel. Therefore, the parametric distributions fitted in R to each of the individual transitions using the code from Williams et al, 2017, had to be implemented in MS Excel.[18] While Williams et al developed a fully R-based model that deals with time continuously, time in Excel is modelled through discrete time cycles. This meant that the approach described in Williams et al had to be modified to be compatible with an Excel-based economic model. As such, the transition probabilities are combined using the rate of the exponential distribution to correct for competing risk (CS, B.3.3.2, Page 79). To ensure validity, the resulting state occupancy per health state over time estimated by the Excel model was validated with the results obtained in the R model as per Williams et al.

a) Please note that cells J12/K12/L12 refer to instantaneous hazards, not transition probabilities. To correct for competing risks, we use the exponential distribution. In the exponential distribution the instantaneous hazard / transition probability equals the rate:

$$Instantaneous\ hazard\ (t) = \frac{f(t)}{S(t)} = \frac{\lambda\, e^{-\lambda t}}{1\ -\ (1\ -\ e^{-\lambda t})} = \frac{\lambda\, e^{-\lambda t}}{e^{-\lambda t}} = \lambda$$

Then to calculate the transition probability while correcting for competing risk, we calculate the total chance of staying (survival), where λ_i is transition probability i:

$S(t) = e^{-\lambda t} = e^{-(\lambda_1+\lambda_2+\lambda_3)\,t}$

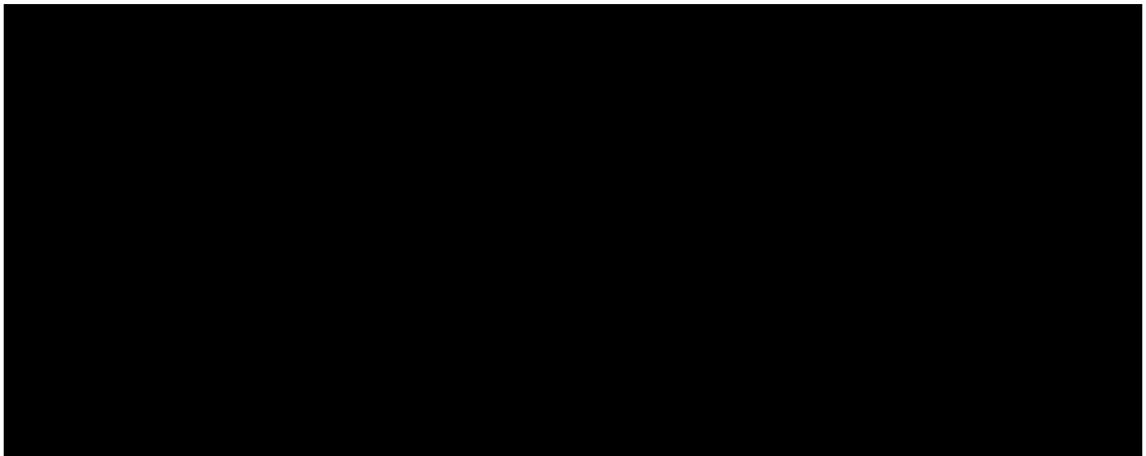
Since we are interested in the chance of leaving, we take 1 – S(t) = $1 - e^{-(\lambda_1+\lambda_2+\lambda_3)\,t}$.

The final part is taking the percentual chance of leaving for that transition: $\frac{\lambda_1}{\lambda_1+\lambda_2+\lambda_3}$ and multiplying that with the total probability of leaving.

b) Using the competing risk method when there is no competition indeed gives a small difference versus using the instantaneous hazard directly, see Figure 9: Survival in TP4 for different modelling approaches

c) . However, since the difference between the two approaches is negligible, we choose for consistency between the Excel-formulas.

Figure 9: Survival in TP4 for different modelling approaches



Health-related quality of life

B16. CS, Section 3.4.2, pages 113-117. Please provide the number of patients included from each group in the RMME models. Please also provide a comparative complete case analysis using only patients for whom all QoL observations were measured.

Response: The number of patients included in each group in the RMME models is provided in Table 10.

Table 10: Number of patients included in the RMME model

	Preferred model (Original)		Preferred model (complete case analysis)	
	Osimertinib	Placebo	Osimertinib	Placebo
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: RMME, repeated measures mixed effect.

A comparative complete case analysis is one approach to address missing longitudinal data. However, when missing observations are missing not at random (MNAR) or missing at random (MAR), a complete case analysis can result in loss of statistical power and produce biased estimates.[19, 20] A complete case analysis can only produce unbiased estimates if observations are missing completely at random (MCAR). Despite the potential bias associated with this method, a comparative complete case analysis was conducted. The results, presented in Table 12 are

consistent with those from the original model, which included all observations (Table 7, and Table 34 in CS).

Table 11: Original model – Parametric estimates

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

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

Table 12: Complete case analysis – Parametric estimates

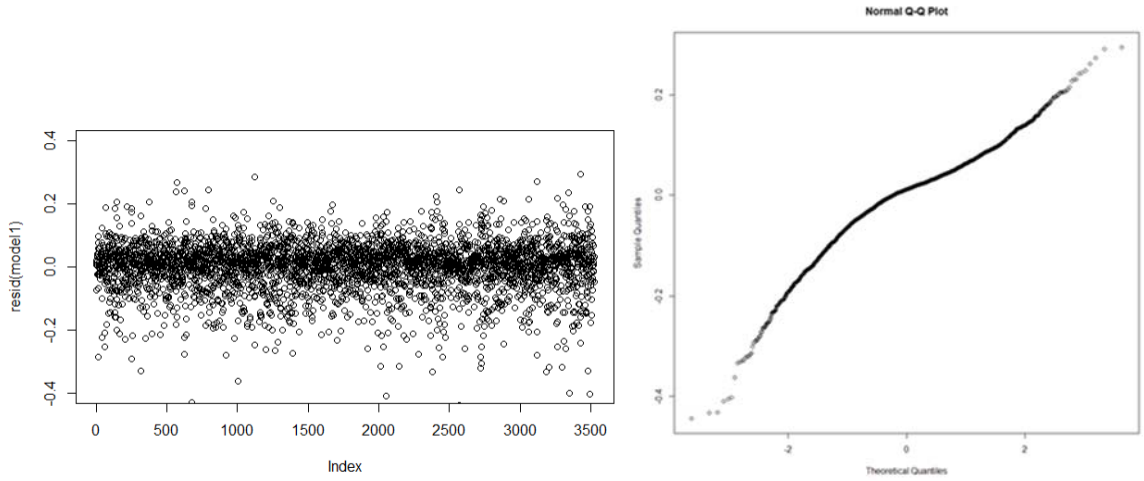
	Estimate	SD
Intercept	[redacted]	[redacted]
Covariate 1 (AE)	[redacted]	[redacted]
Covariate 2 (Baseline)	[redacted]	[redacted]

Abbreviations: AE, adverse event; SD, standard deviation.
* Result was not significant, likely due to the low number of observations ([redacted].

B17. CS Section B.3.4.2.1, pages 113-114. Linear repeated measures mixed effects models make the assumption of normality of model residuals and EQ-5D data are known to be non-normal (and as demonstrated by the mean and CIs in Table 30). Please comment on whether any resulting bias was taken into account and whether any other methods were considered such as adjusted limited dependent variable mixture models (see Alva *et al*, Value in Health, 2012; vol 15(3)) DOI: 10.1016/j.jval.2011.12.014.

Response: The residuals of the RMME model were tested (Figure 10) and although the residuals are not perfectly normally distributed, the differences were deemed not significant enough to skew the results. Therefore, no other methods were considered.

Figure 10: Residuals of the RMME model



Abbreviation: RMME, repeated measures mixed effect.

B18. CS, Section 3.4.2.2., Figure 39, page 115. [redacted]

Response: A t-test was performed in R to test whether the EQ-5D utility values were significantly different in the observations after Week 144. The results of the t-test, provided below (Figure 11), determined this numerical drop was not significantly different. Note that there were only 44 placebo patients and 57 osimertinib patients with HRQoL observations after Week 144.

Figure 11: Results of HRQoL t-test

[redacted]

B19. CS, Section 3.4.2.2, Table 32, page 116 and Table 33, page 117. Please provide the R summary (model) output for all of the models reported in these tables and also for a null model.

Response: Data are provided in Appendix B.

B20. Priority question. CS, Section 3.4.6, Table 38, page 128. Whilst the model includes the adjustment of health utility for increasing age, the model consistently suggests that in the DF and LRR states, health utility is better for people with NSCLC compared with the general population in every model cycle. Please justify this assumption. Please also clarify why people with LRR are assumed to have no loss in HRQoL compared with either those in DF or the general population.

Response: UK clinical experts consulted in interviews confirmed that it is likely a significant proportion of patients will achieve a 'functional cure' following complete surgical resection for early stage EGFRm-positive NSCLC and therefore will reach their normal life expectancy and die from causes unrelated to NSCLC. Given this, it is not clinically implausible for patients in the DF setting to achieve a utility estimate similar to the general age-matched population for England, with the value estimated in ADAURA (0.825), slightly higher than the age-matched general population in England (0.810).[21]

The post-hoc exploratory analysis of ADAURA HRQoL, described in response to A7, compared baseline SF-36 health domain T-scores with the general population.[8] The majority of health domains were found to be comparable with the general population (within ±0.3 standard deviation [SD] of the normative mean), while lower T-scores (0.4–0.9 SD below the normative mean) were observed only in Role-physical, Social functioning, and Role-emotional.

Nafees et al, 2017, also reported that the utility of NSCLC patients of all ages with stable disease and no AEs is 0.84, which is higher than the utility value used for the DF health state in the current model and offers further validation of the choice of utility value.[22]

A scenario analysis has been conducted where 0.810 health state utility is applied in the DF health state. The impact of the ICER is minimal. This amendment is included in the updated base case presented by the Company in Appendix A.

The health state utility in the LRR health state was set equal to the DF state value due to a lack of data in patients with LRR in the ADAURA trial. This simplifying assumption was made due to lack of published QoL data for patients in the LRR

state, although in clinical practice it may be anticipated that patients have a lower utility with LRR (CS, Section B.1.3.2.2).

Due to the overall lack of published QoL data for patients in the LRR state, in the updated base case analysis the LRR utility value remains equal to that assumed for DF, now 0.810 (Appendix A). This has been acknowledged as a limitation of the economic analysis.

B21. Model, worksheets “Tracecomp1” and “Tracecomp0.” The model applies disutilities from Nafees *et al* in the first model cycle. Is the model assuming that these health losses apply for a full year or just the first 28-day cycle?"

Response: The disutilities applied in cycle 0 account for the quality-of-life decrement due to the AEs associated with osimertinib and placebo as reported in the ADAURA trial. The values used on worksheets ‘Trace Comp1’ and ‘Trace Comp0’ in the first model cycle (updated to 30.44 days) take into account the total disutility incurred over duration of treatment.

Costs

B22. CS, Section 3.5.2.5., page 128. The model does not include any monitoring costs for patients receiving adjuvant/metastatic osimertinib. However, monitoring costs are included for other treatments. Clinical advice received by the ERG indicates that patients receiving osimertinib would require the same blood tests as for PDC (which should be the same for docetaxel) as well as ECGs. Please amend the model, or provide a justification for the exclusion of these costs.

Response: Monitoring costs included in the model have been revised based on data available from clinical trials (ADAURA, FLAURA) and above suggestions – please see Table 13 below for the updated monitoring tests and costs included for each treatment. Monitoring tests with a frequency of ≤12 weeks were included based on the above trials. For osimertinib, ADUARA and FLAURA provided data for monitoring conducted in the adjuvant and metastatic settings, respectively. For TKIs, such as erlotinib, gefitinib and afatinib, monitoring data were obtained from the FLAURA trial. Information on monitoring was however not available for ABCP from the

IMPower150 trial publications, and therefore it was assumed that this would require the same monitoring as PDC.

These amended monitoring costs are now included in the updated base case presented by the Company in Appendix A.

Table 13: Monitoring tests and costs in the updated model

Regimen	Test	Average number of tests per model cycle	Unit cost	Cost per model cycle	Source for resource use (RU) and costs (C)
Osimertinib – DF state	Liver function test	0.36*	£1.10	£131.38	RU: ADAURA C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Renal function test	0.36*	£1.10		RU: ADAURA C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Complete blood count	0.36*	£2.79		RU: ADAURA C: NHS Reference costs 2018/19, DAPS05 – Haematology
	ECG	0.36*	£102.35		RU: ADAURA C: NHS Reference costs 2018/19, EY51Z - Electrocardiogram Monitoring or Stress Testing
	Echocardiogram	0.36*	£257.61		RU: ADAURA C: NHS Reference costs 2018/19, EY50Z – Complex Echocardiogram
Osimertinib – DM state	Liver function test	0.72†	£1.10	£262.76	RU: FLAURA C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Renal function test	0.72†	£1.10		RU: FLAURA C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Complete blood count	0.72†	£2.79		RU: FLAURA C: NHS Reference costs 2018/19, DAPS05 – Haematology
	ECG	0.72†	£102.35		RU: FLAURA

Regimen	Test	Average number of tests per model cycle	Unit cost	Cost per model cycle	Source for resource use (RU) and costs (C)
					C: NHS Reference costs 2018/19, EY51Z - Electrocardiogram Monitoring or Stress Testing
	Echocardiogram	0.72†	£257.61		RU: ADAURA C: NHS Reference costs 2018/19, EY50Z – Complex Echocardiogram
Erlotinib/ Gefitinib/ Afatinib	Liver function test	0.72†	£1.10	£262.76	RU: FLAURA C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Renal function test	0.72†	£1.10		RU: FLAURA C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Complete blood count	0.72†	£2.79		RU: FLAURA C: NHS Reference costs 2018/19, DAPS05 – Haematology
	ECG	0.72†	£102.35		RU: FLAURA C: NHS Reference costs 2018/19, EY51Z - Electrocardiogram Monitoring or Stress Testing
	Echocardiogram	0.72†	£257.61		RU: FLAURA C: NHS Reference costs 2018/19, EY50Z – Complex Echocardiogram
PDC	Liver function test	1	£1.10	£4.99	RU: Assumption C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Renal function test	1	£1.10		RU: Assumption C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Complete blood count	1	£2.79		RU: Assumption C: NHS Reference costs 2018/19, DAPS05 – Haematology
Docetaxel	Liver function test	1	£1.10	£4.99	RU: Assumption

Regimen	Test	Average number of tests per model cycle	Unit cost	Cost per model cycle	Source for resource use (RU) and costs (C)
					C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Renal function test	1	£1.10		RU: Assumption C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Complete blood count	1	£2.79		RU: Assumption C: NHS Reference costs 2018/19, DAPS05 – Haematology
ABCP	Liver function test	1	£1.10	£4.99	RU: Assumption C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Renal function test	1	£1.10		RU: Assumption C: NHS Reference costs 2018/19, DAPS04 – Clinical biochemistry
	Complete blood count	1	£2.79		RU: Assumption C: NHS Reference costs 2018/19, DAPS05 – Haematology

Abbreviations: ABCP, atezolizumab, bevacizumab, carboplatin, paclitaxel; DF, disease-free; DM, distant metastasis; ECG, electrocardiogram; PDC, pemetrexed, cisplatin.
*Calculated based on an average frequency of 12 weeks of tests conducted.
†Calculated based on an average frequency of 6 weeks of tests conducted.

B23. CS, Section 3.5.2.2., Table 41, page 124. The model assumes that LRR is treated using 3 cycles of PDC plus one dose of brachytherapy. Clinical advice received by the ERG indicates that patients would receive either chemoradiation or radiotherapy alone, and in both cases patients would receive 3-4 weeks of daily external beam radiotherapy. Please consider revising this aspect of the model.

Response: The cost of chemoradiation and single-agent radiotherapy in economic model has been amended to include external beam radiotherapy, instead of brachytherapy.

The cost of external beam radiotherapy (EBRT) comprised of a unit cost per fraction and a one-off cost for a planning meeting (Table 14). The dosage for radiotherapy

was sourced from the NICE guideline (NG122) on diagnosis and management of lung cancer. Although EBRT requires several trips to the hospital for treatment, incurring time and travel costs for patients, the analysis was undertaken from the NHS and PSS perspective and therefore additional costs were conservatively not included.

Table 14: Updated radiotherapy costs in LRR

Cost input	Unit cost	Number of units	Total cost per cycle	Source
External beam radiotherapy – cost per fraction	£127.31	20 fractions (55 Gy in 20 fractions over 4 weeks)	£3,391.17	NHS reference costs 2018/19, SC3Z, Outpatient – Deliver a Fraction of Complex Treatment on a Megavoltage Machine
Cost per planning meeting	£845.00	1		NHS reference costs 2018/19, SC5Z, Outpatient – Preparation for Complex Conformal Radiotherapy, with Technical Support

B24. CS, Section 3.5.2.2., Table 41, page 124. The model assumes that LRR is exclusively treated with chemoradiation. Why does the model not include the possibility of surgery alone, or radiotherapy alone? Please consider revising this aspect of the model.

Response: UK clinical experts stated that the vast majority of patients with stage IB–IIIA EGFRm NSCLC receive chemoradiation when they progress to the loco-regional disease state. Chemoradiation is therefore considered the standard of care in routine clinical practice. The use of single-agent radiotherapy is low and varies across the UK. Upon validating the treatment pathway with clinicians, less than 18% of patients with stage IB–IIIA EGFRm NSCLC would receive single-agent radiotherapy and a negligible proportion would receive surgery.

A scenario analysis was conducted where single-agent radiotherapy was included as a treatment for patients with LRR. Following engagement with UK clinical experts, this amendment is included in the updated base case presented by the Company in Appendix A. Due to the very low number of patients that undergo surgery in the loco-regional disease state, no scenario analysis has been conducted as it not considered standard practice.

B25. CS, Section 3.5.3., Table 49, page 132. The ERG's clinical advisors noted that stereotactic radiotherapy used to treat CNS metastases usually involves one dose (rather than six) and whole brain radiotherapy normally involves two or more doses (rather than one). Please justify the number of doses chosen and consider revising this aspect of the model.

Response: The number of doses chosen for stereotactic radiotherapy and whole brain radiotherapy to treat CNS metastases was derived from the NICE TA536.[24] The number of doses were accepted by the ERG, NICE committee and clinical advisor(s) in this appraisal.

In this submission, the assumed number of doses of stereotactic radiotherapy and whole brain radiotherapy were validated with six UK clinicians consulted through interviews.

Nonetheless, a scenario analysis where the number of doses for stereotactic radiotherapy and whole brain radiotherapy are in line with the ERG's clinical advisors has been explored (one dose and two doses, respectively). The updated ICER increased from £11,136 to £11,361 (Appendix A, Table 6).

B26. Priority question. CS, Section B.3.5.5., page 134. The model applies the cost of a single EGFR test (£208.98) per patient treated with osimertinib. However, approximately 10 patients will need to be tested in order to identify a patient with the EGFR mutation. Please include the costs associated with the number needed to test to identify a positive case.

Response: The Company acknowledge that the number needed to test may need to be accounted for in the calculation of the cost of testing for EGFR mutations. UK clinicians consulted in interviews indicated that a proportion of patients are already routinely tested for EGFR mutations in NHS clinical practice. However, clinicians noted that testing rates varied geographically, with some regions routinely testing all NSCLC patients undergoing surgical resection. Therefore, as an assumption, the cost of EGFRm testing was not adjusted to include the number needed to test. Furthermore, clinicians advised that many patients undergo REFLEX testing for a range of biomarkers as part of a next generation sequencing panel, such as EGFR, ALK mutations and PDL1 status. The running of the next generation sequencing

panel has one cost, irrespective of the number of type of tests requested by the requesting clinician. Therefore, if not already requested, clinicians advised that they could request for EGFR testing to be conducted as part of this, and therefore no additional costs would be incurred.

A scenario analysis was conducted whereby the total cost of EGFRm testing is derived from the unit cost of testing (£208.98), multiplied by the number needed to test to detect one patient with a confirmed EGFR mutation. The number of tests needed to detect one patient with EGFR mutation was estimated at 10 (1 divided by the prevalence rate of 10%). Therefore, in this scenario, the total per-patient cost of EGFRm testing is £2,089.80. Whilst conservative, the amended cost has been included as part of the updated base case analysis (Appendix A)

B27. CS, Section B.3.5.4, page 133. Please clarify why AE costs associated with treatments for loco-regional and distant recurrence have not been included in the model.

Response: AE costs were included from the ADAURA trial in the DF state, however, for the LRR and DM states, a conservative assumption was applied by not including AE costs in these states. Due to the treatment pathways in both arms and because more patients in the placebo arm reach the LRR and DM states earlier than in the osimertinib arm, it would be anticipated that AE costs in the placebo arm would be higher.

B28. CS, Section 3.6.1., Table 52, page 138. Please explain why vial sharing has been assumed for chemotherapy?

Response: It is anticipated that on average almost no wastage would be left from vials used for chemotherapy in hospitals as there would be an attempt to optimise the treatments given to patients on a day. However, a scenario was performed to evaluate the effect of including vial wastage costs in the model, which found wastage had a minimal impact on the ICER. Vial wastage costs have been included as part of the updated base case analysis (Appendix A)

B29. CS, Section 3.5.2.2., page 124. Please clarify why other concomitant drugs have not been included in the model e.g. G-CSF and anti-emetics. Please consider including these in the model.

Response: The vast majority of patients who receive targeted TKI therapy do not require supportive care treatments and the use of anti-emetics is not common practice as the risk of patients experiencing nausea is low. [redacted].[11] Therefore, concomitant drugs have not been considered for inclusion in the model. Anti-emetic drugs are low-cost treatments and therefore the impact of concomitant drugs is expected to be negligible.

Model results and analysis

B30. Priority question. CS, Section B.3.3.6, Figure 38, page 112. Based on a visual comparison of the Kaplan-Meier plot and the modelled OS function, the economic model appears to be under-predicting OS in the comparator group. Please comment.

Response: As discussed through CS, Section B.3.3, the chosen final parametric models were selected based on a visual inspection of the combined DFS and OS curves, such that they achieve a good fit to the observed data and are deemed valid and realistic by UK clinical experts. However, there is still a level of uncertainty in the long-term extrapolations due to the significant immaturity of the ADAURA OS data at the time of the data cut-off (4.3% maturity). At the time of data cut-off, only 2.7% of patients in the osimertinib arm and 5.8% in placebo arm had died.

[redacted]

The long-term extrapolated ADAURA OS curves were validated with external clinical data in patients with early-stage, resected NSCLC. As discussed in CS, Section B.3.3.6, at around 8 years of follow up, the ANITA trial's placebo arm reached

~35−40% OS rate, which is also comparable to the model estimated OS results (after the application of the cure assumption).

B31. Priority question. CS, Section B.3.7, Table 54, page 149 and Section B.3.8, Table 57, page 151. There is a noticeable difference in the mean QALYs between the deterministic and probabilistic versions of the model. Please explain the reasons for this difference.

Response: This was due to an error in the calculation of age-adjusted utilities in the probabilistic sensitivity analysis (PSA). Please note that the deterministic analysis was absent of this error. In the PSA, the age-adjusted utilities are sampled using a beta-distribution to avoid "flipping" of the value (i.e. coefficients stay negative). However, since the results of the beta-distribution were incorrectly not multiplied by −1, the coefficients became positive in the PSA and with that, led to increasing utility with increasing age. This has now been corrected in the model with details of the amendment provided below (Table 15).

Table 15: Correction to age-adjusted utilities calculation in the PSA

Cell	Old formula	New formula
Parameters! P26	=IFERROR(CHOOSE(MATCH(K26, PSA.Dist,0),NORM.INV(L26,F26,M26), EXP(NORM.INV(L26, LN(F26),M26)),IF(F26=0,0,GAMMA.INV(L26,$Q26,$R26)),BETA.INV(L26,N26,O26)),F26)	=-1*IFERROR(CHOOSE(MATCH(K26, PSA.Dist,0),NORM.INV(L26,F26,M26), EXP(NORM.INV(L26, LN(F26),M26)),IF(F26=0,0,GAMMA.INV(L26,$Q26,$R26)),BETA.INV(L26,N26,O26)),F26)
Parameters! P27	=IFERROR(CHOOSE(MATCH(K27, PSA.Dist,0),NORM.INV(L27,F27,M27), EXP(NORM.INV(L27, LN(F27),M27)),IF(F27=0,0,GAMMA.INV(L27,$Q27,$R27)),BETA.INV(L27,N27,O27)),F27)	=-1*IFERROR(CHOOSE(MATCH(K27, PSA.Dist,0),NORM.INV(L27,F27,M27), EXP(NORM.INV(L27, LN(F27),M27)),IF(F27=0,0,GAMMA.INV(L27,$Q27,$R27)),BETA.INV(L27,N27,O27)),F27)

Abbreviation: PSA, probabilistic sensitivity analysis.

The Company conducted an independent model QC and Table 1 in Appendix A lists all the model corrections.

Executable model

B32. Priority question. Model, general. The version of the executable model received by the ERG frequently crashes when parameter values are amended. Please explore whether it is possible to reduce the memory requirements of the model to make it more stable. Note - it is likely that the source of the problem is the user-defined function used to estimate cumulative survival probabilities.

Response: The Company would like to apologise for any inconvenience encountered when using the economic model. The economic model was developed by several health economists and was tested by multiple parties on a standard professional laptop (i7 processor, 8GB RAM) without any issues or crashing. Nevertheless, we have made several changes to the model to reduce its memory size, including the suggested amendment to the user-defined functions for cumulative survival probabilities.

B33. Model, worksheets “Trace Comp0” and “Trace Comp1”. The model trace is drawn from the “mid-cycle” calculations in the “TP matrix comp” worksheets. For the first model cycle, the trace is using the uncorrected values (whereby all patients are in DFS at the beginning and the end of the cycle). This is counting the first cycle twice. Please confirm that this is an error and correct the model.

Response: The Company acknowledge that this was an error in the model. Please find details of the correction below (Table 16).

Table 16: Correction to model cycle calculations

Cell(s)	Old formula	New formula
TP Matrix Comp0!BJ:BS	=AJ11 (start of cycle [t])	=AJ12 (start of cycle [t+1])
TP Matrix Comp1!BN:BY	=AJ11 (start of cycle [t])	=AJ12 (start of cycle [t+1])

The Company conducted an independent model QC and Table 1 in Appendix A lists all the model corrections.

B34. Priority question. Please provide an updated model which includes clearer labelling of the evidence source (including the specific trial arm) for each survival model included in worksheet "STM_Surv."

Response: The labelling in the worksheet "STM_Surv" has been updated, where for each individual transition the source and the arm of the trial is now clearly stated.

B35. Model, worksheet "Resources". The calculations in this worksheet include a variable called "cycles_per_year" which takes the value of 13. However, this implies that there are 364 days per year (13 x 28). Please clarify why this was assumed and update the model to assume that there are 365.25 days per year.

Response: Please refer to Company response in B36.

B36. Model, worksheets "TP Matrix Comp0" and "TP Matrix Comp1", columns D and E. These calculations assume that there are 52 weeks in a year. However, there are 52.18 weeks per year. Please clarify why this was assumed and update the model to assume that there are 52.18 weeks per year.

Response to B35 and B36:

The cycles per year in the economic model were calculated based on the number of weeks in a year and the assumed cycle length. For rounding simplification, the number of weeks in a year was assumed to be 52 weeks (and 364 days per year). This translated into 13 cycles per year.

The economic model has been updated to assume there is 52.18 weeks and 365.25 days per year. This now translates into 13.18 cycles per year.

B37. Model, worksheets "TP Matrix Comp0" and "TP Matrix Comp1", column H. The model assumes that a constant proportion of surviving patients are men in all model cycles, yet the life tables indicate that men and women have different age-specific mortality rates, which means that this cannot be true. Please clarify why this assumption was made. Please update the general population mortality risks weighted according to the proportion of men and women at model entry.

Response: The proportion of male vs female was kept constant throughout the model time horizon to avoid adding further complexity to the economic model. The

alternative, separately tracking the survival of males and females, would have significantly increased the model size.

The proportion split of male and female at model entry is not a significant driver of the model and tracking the two separately is likely to have a minimal impact on the model. Scenario analyses were conducted below that explore the impact of modelling a 100% female and 100% male population based on the updated base case analysis. The ICER minimally varied, from £12,280 with a 100% male population to £10,675 in a 100% female population (Appendix A, Table 6).

Please note that although women have a better OS in the general population (thus resulting in a lower ICER), the [redacted].

B38. Model, worksheet "STM_Surv", all columns labelled "instant hazards". The first row of these calculations (e.g. cell H28) uses the difference between the cumulative hazard for each endpoint at times t1 and t0. All subsequent rows calculate probabilities as one minus the probability at time t+1 divided by the probability at time t. Please clarify why these columns include estimates of instantaneous hazards and 28-day event probabilities at different timepoints. Please also clarify why the same data points are being used in the first and second rows of each of these columns (e.g. the calculation in cell H28 uses the cumulative survival probabilities from cells BG25 and BG26, and so too does the calculation in cell H29).

Response: The formulas in the worksheet "STM_Surv" initially used cycle probabilities instead of instantaneous hazards to ensure the probabilities in the matrices summed up to 1 (e.g. column TP Matrix Comp0!AV). This worksheet has now been updated to use the instantaneous hazard at all time points (Table 17).

Table 17: Correction to instantaneous hazards in model

Cell	Old formula	New formula
STM_Surv all instant hazard columns	=1-BS28/BS27 (1- probability at time t+1 dived by probability at time t)	=K15-K14 (cum haz[t-1] – cum haz[t])

The Company conducted an independent model QC and Table 1 in Appendix A lists all the model corrections.

B39. Priority question. Model, worksheet "TP Matrix Comp1" columns VR to APQ (DM1 sub-model). The formulae in this sub-model for all timepoints after model entry refer to the unadjusted values for TP7 (DM1 to dead). Please confirm that this is an error and correct the model. Please also correct the accompanying incident death calculations (rows 535 to 1056).

Response: The Company acknowledge that this was an error in the model. Please find details of the correction below (Table 18).

Table 18: Correction to DM1 sub-model

Cell	Old formula	New formula[t]
TP Matrix Comp0!AV	=IFERROR(WI10*(1-INDEX($AD$10:$AD$530,WJ$9)-MAX(INDEX($H$10:$H$530,$B11+1),INDEX($P$10:$P$530,WJ$9))),999)	=IFERROR(WI10*(1-INDEX($AD$10:$AD$530,WJ$9)-MAX(INDEX($H$10:$H$530,$B11+1),INDEX($AE$10:$AE$530,WJ$9))),999)

[t]This is adjusted in the whole DM1 sub-block (including the accompanying incident death calculations).

B40. Model, worksheets "TP Matrix Comp0" and "TP Matrix Comp1". In worksheet "TP Matrix Comp0" cell X76 and "TP Matrix Comp1" cell U75, the first value in which a non-zero cure proportion is given is 0.3167. Please confirm that this is an error and correct the model.

Response: The Company acknowledge that this was an error in the model. Please find details of the correction below (Table 19).

Table 19: Correction to non-zero cure proportion

Cell	Old formula	New formula[t]
TP Matrix Comp0!X	=IF(OR(apply_cure<>"Yes",$D13<start_cure),0,IF($D13>start_cure+cure_warmup,cure_end_percentage,cure_end_percentage*($D13-(start_cure-1))/((2+start_cure+cure_warmup)-(start_cure-1))))	=IF(OR(apply_cure<>"Yes",$D13<start_cure_tagrisso),0,IF($D13>start_cure_tagrisso+cure_warmup_tagrisso,cure_end_percentage_tagrisso, (cure_end_percentage_tagrisso-start_cure_percentage_tagrisso)*($D13-(start_cure_tagrisso-1))/((2+start_cure_tagrisso+cure_warmup_tagrisso)-(start_cure_tagrisso-1))+start_cure_percentage_tagrisso))

[t]This is updated both in TP Matrix Comp0 and TP Matrix Comp1.

The Company conducted an independent model QC and Table 1 in Appendix A lists all the model corrections.

B41. Model, worksheets "TP Matrix Comp0", columns AG and AH. The competing risk adjustments in these columns include an =MAX()function which is not included in any of the other competing risk adjustments in either treatment group. This also appears to be incorrect given these event risks are conditioned on time since state entry rather than time since model entry. Please clarify and correct the model if appropriate.

Response: This functionality was superseded after having separate matrices for death transitions. The maximum functions were taken out as detailed below (Table 20).

Table 20: Removal of maximum functions

Cell	Old formula	New formula[t]
TP Matrix Comp0!X	=Max() function included in competing risks derivation of columns AG and AH	=Max() function removed from competing risks calculations in columns AG and AH

[t]This is updated both in TP Matrix Comp0 and TP Matrix Comp1.

The Company conducted an independent model QC and Table 1 in Appendix A lists all the model corrections.

B42. Priority question. Model, worksheet "STM_Surv". Within the adjuvant osimertinib treatment group, the no re-treat and re-treat probabilities for DM1 to DM2 (columns Q and AW) are both drawn from the control arm of FLAURA. Was this intentional? If so, please justify the assumption. If not, please correct the model.

Response: The Company acknowledge that this was an error in the model. Please find details of the correction below (Table 21).

Table 21: Correction to DM1 and DM2 treatment probabilities

Cell	Old formula	New formula
STM_Surv!AW	=-LN(CK25)	=-LN(CM25)

The Company conducted an independent model QC and Table 1 in Appendix A lists all the model corrections.

B43. Model, worksheet “Trace Comp0”, column AJ. The values in this column are not multiplied by the model trace and stop at 3 years. Please confirm that these are errors and correct the model.

Response: This is not an error in the model. In this column the osimertinib drug costs in the DF health state are calculated, where the cost of osimertinib per cycle is multiplied by the time to treatment discontinuation. As osimertinib is given for 3 years (that is, until treatment stops), the formula explicitly stops after 3 years. In ADAURA patients received osimertinib (or placebo) for 3 years or until disease recurrence or fulfilment of a criterion for treatment discontinuation.

B44. Priority question. Model, worksheets “Trace Comp0” and “Trace Comp1” (multiple cost calculations). The model calculates the costs of LRR by transforming the cost of a finite number of treatment cycles into a cyclical cost (e.g. in “Clinical inputs” cell F18). Given that the LRR sub-model already tracks the number of people in each state at each timepoint (i.e. 1, 2, and 3 cycles after LRR), please clarify why this simplification was required. Please revise this approach to calculate costs directly from the number of patients in LRR in the first three cycles of the LRR sub-model. Please also apply the same logic to other treatment costs in the DM1 and DM2 sub-models.

Response: Given that the economic model has 5 health states with some tunnel states modelled, we chose to implement the cost calculations only on the final (mid-cycle) traces to avoid bulky cost calculations on the matrices themselves. However, this has been updated as suggested (Table 22).

Table 22: Update to LRR cost calculations

Cell	Old formula	New formula[i]
Trace Comp0!AP9	=K9*cost_drug_acquisition_lr_tx0	=SUMIF('TP Matrix Comp0'!$BZ$10:$VZ$10,"<="&'Clinical inputs'!$G$16,'TP Matrix Comp0'!BZ11:VZ11)*'Clinical inputs'!$K$16

[i]This formula was applied for the LRR, DM1 and DM2 health state in both Trace Comp0 and Trace Comp1.
Abbreviation: LRR, loco-regional recurrence.

B45. Please clarify why in both treatment arms, the cost of subsequent drug administration applied in DM1 is £1. Please confirm that this is an error and correct

the model. Please also ensure that the administration costs of osimertinib are included for the re-treated patients.

Response: The Company acknowledge that this was an error in the model. This was a result of a multiplication where the first input was not multiplied (causing the whole chain to be shifted). Please find details of the correction below (Table 23).

Table 23: Correction to subsequent drug administration in DM1

Cell	Old formula	New formula
Parameters!E67 and Parameters!E68	=IF('Clinical inputs'!J36="",'Clinical inputs'!I36,'Clinical inputs'!J36)+ IF('Clinical inputs'!J37="",'Clinical inputs'!I37,'Clinical inputs'!J37)*cost_drug_admin_dm1_osimertinib_subsequent_cycles+ IF('Clinical inputs'!J38="",'Clinical inputs'!I38,'Clinical inputs'!J38)*cost_drug_admin_dm1_Erlotinib_subsequent_cycles+ IF('Clinical inputs'!J39="",'Clinical inputs'!I39,'Clinical inputs'!J39)*cost_drug_admin_dm1_Gefitinib_subsequent_cycles+ IF('Clinical inputs'!J40="",'Clinical inputs'!I40,'Clinical inputs'!J40)*cost_drug_admin_dm1_Afatinib_subsequent_cycles+ IF('Clinical inputs'!J41="",'Clinical inputs'!I41,'Clinical inputs'!J41)*cost_drug_admin_dm1_PDC1_subsequent_cycles+ IF('Clinical inputs'!J42="",'Clinical inputs'!I42,'Clinical inputs'!J42)*cost_drug_admin_dm1_PDC2_subsequent_cycles+ IF('Clinical inputs'!J43="",'Clinical inputs'!I43,'Clinical inputs'!J43)*cost_drug_admin_dm1_PDC3_subsequent_cycles	=IF('Clinical inputs'!J36="",'Clinical inputs'!I36,'Clinical inputs'!J36)*cost_drug_admin_dm1_osimertinib_subsequent_cycles+ IF('Clinical inputs'!J37="",'Clinical inputs'!I37,'Clinical inputs'!J37)*cost_drug_admin_dm1_Erlotinib_subsequent_cycles+ IF('Clinical inputs'!J38="",'Clinical inputs'!I38,'Clinical inputs'!J38)*cost_drug_admin_dm1_Gefitinib_subsequent_cycles+ IF('Clinical inputs'!J39="",'Clinical inputs'!I39,'Clinical inputs'!J39)*cost_drug_admin_dm1_Afatinib_subsequent_cycles+ IF('Clinical inputs'!J40="",'Clinical inputs'!I40,'Clinical inputs'!J40)*cost_drug_admin_dm1_PDC1_subsequent_cycles+ IF('Clinical inputs'!J41="",'Clinical inputs'!I41,'Clinical inputs'!J41)*cost_drug_admin_dm1_PDC2_subsequent_cycles+ IF('Clinical inputs'!J42="",'Clinical inputs'!I42,'Clinical inputs'!J42)*cost_drug_admin_dm1_PDC3_subsequent_cycles+ IF('Clinical inputs'!J43="",'Clinical inputs'!I43,'Clinical inputs'!J43)*cost_drug_admin_dm1_PDC4_subsequent_cycles

B46. Model, worksheet "Trace Comp0", column AV. The model applies the administration cost of docetaxel to patients who are retreated in state DM2 (column N2). Please confirm that this is an error and correct the model if appropriate.

Response: Please refer to Company response in B48.

B47. Model, worksheet “Trace Comp0”. Please clarify why drug administration costs for PDC in DM1 are applied to patients who are in the 're-treat' state (column L) and not to 'no re-treat'. Please confirm that this is an error and correct the model if appropriate.

Response: Please refer to Company response in B48.

B48. Model, worksheet “Trace Comp0”. Please clarify why drug administration costs of PDC are not applied to patients in DM2. Please that confirm this is an error and correct the model if appropriate.

In response to B46, B47 and B48:

The Company acknowledge that these were errors in the model. Please note that the drug administration costs were not corrected for length of treatment, which particularly affected the LRR health state, due to the high administration costs incurred in this health state (Table 24).

Table 24: Correction to length of treatment

Cell	Old formula	New formula
Trace Comp0!BA (all cells)	=N9*cost_drug_admin_dm2_first_cycles_total_tx0	='TP Matrix Comp0'!BZ11*cost_drug_admin_lr_first_cycles_total_tx0+SUM('TP Matrix Comp0'!CA11:VZ11)*cost_drug_admin_lr_subsequent_cycles_total_tx0

Note that the named range “cost_drug_admin_dm2_subsequent_cycles_total_tx0_retreatment” has created in Parameters.

The Company conducted an independent model QC and Table 1 in Appendix A lists all the model corrections.

Section C: Data and analysis requests

C1. Priority question. Data request. For each transition within the model, please provide the corresponding Kaplan-Meier summary data to enable the ERG to reproduce the graphical plots (the timepoint and probability, and the lower and upper values of the 95% confidence intervals). Please also provide the corresponding observed hazard plots (such as those produced by the R package ‘muhaz’) for each

transition and the data required to recreate these plots (the timepoint and estimated hazard).

Response: Data has been provided in Appendix C.

C2. Priority question. Analysis request. Please provide the results of an analysis in which no re-treatment is assumed and in which all patients in both groups enter the model in the DM1 state. Please comment on whether the results of this comparison of osimertinib versus chemotherapy are consistent with the results used to inform decision-making in NICE TA664. Does osimertinib appear to be cost-effective? Note – the ERG was unable to perform this analysis as the model frequently crashes.

Response: The ERG's request to re-evaluate the cost-effectiveness of osimertinib in locally advanced locally advanced or metastatic EGFRm NSCLC is out of scope for this appraisal. Osimertinib has already received a positive recommendation from NICE for untreated locally advanced or metastatic EGFRm NSCLC (TA654) and thus re-evaluating its cost-effectiveness at this stage would be inappropriate.

Furthermore, a comparison of the cost-effectiveness of osimertinib in the locally advanced or metastatic setting between the model submitted in TA654 and the economic model for this appraisal would be subject to a high level of bias. Firstly, the two economic models are using different data cuts from the FLAURA trial. The cost-effectiveness model in TA654, submitted in 2018, was populated with the first data cut (DCO1) from the FLAURA trial. The DM health states in this model have been populated with FLAURA data from the second and final data cut (DCO2).

Secondly, the structures of the two economic models differ, with a partitioned survival model developed in TA654, whereas the survival outcomes estimated in this appraisal being based on a multi-state model framework (CS, Section B.3.3.1.1). A recent study comparing the cost-effectiveness estimated via a partitioned-survival analysis and a multi-state model indicated that the difference in model structure had a significant impact on predicted outcomes and cost-effectiveness results.[25] There are further differences between the two models, including different parametric model types (standard individual parametric model versus piecewise parametric model) and vastly different treatment pathways.

Therefore, the requested analysis is considered to be inappropriate and therefore has not been provided.

Nevertheless, a comparison was conducted of the long-term OS extrapolations in patients with locally advanced or metastatic disease predicted in the economic model for this appraisal versus the FLAURA partitioned survival model populated with DCO2 data.

The structure of the economic model for this appraisal was modified so that all patients started in the DM1 health state. All transitions in this model (TP6, TP7 and TP8) were modelled using FLAURA DCO2. The resulting OS graph is compared to the partitioned survival model with FLAURA DCO2 data (Figure 12). The Weibull parametric model was selected to model OS in each cost-effectiveness model. The predicted OS from the ADAURA model is generally similar to that predicted in the FLAURA model, with both fitting the KM data well.

Figure 12: Comparison of OS in DM in the ADAURA and FLAURA economic models

While conducting this comparison of OS, an error was identified in the economic model for this appraisal. The error was related to the cycle length used in the DM health states; the parametric distributions were fitted on monthly data while the economic model assumes a cycle length of 4 weeks. This caused a shift in time of ~5% (difference of ~1.5 day per cycle length), which affected the time spent in the DM health states and caused the survival to be underestimated (in both arms). To

rectify this issue, the current model structure was modified so that the cycle length to is now set to one month (equal to ~4.35 weeks). This correction has been applied as part of the update to the Company's updated base case presented in Appendix A, Table 1.

C3. Priority question. Analysis request. Please provide a subgroup analysis to assess the cost-effectiveness of osimertinib 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.[26, 27] 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 57% of patients diagnosed with stage I NSCLC will survive for at least 5 years.[26, 28] 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 61% reduction in the risk of disease recurrence or death (HR: 0.39; 95% CI: 0.18, 0.76) 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 and the early unblinding of the study due to overwhelming efficacy, the data in patients with stage IB disease are highly immature, with just [redacted] events reported in patients receiving osimertinib vs placebo, respectively, at the time of 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. However, as the study was

powered to evaluate the efficacy of patients in the primary population (i.e. patients with stage II−IIIA disease) and overall population (i.e. patients with stage IB−IIIA disease), we have provided a scenario analysis to demonstrate the cost-effectiveness of osimertinib in the primary population i.e. in those with stage II−IIIA disease alone. This analysis excludes patients diagnosed with stage IB disease and therefore enables the relative cost-effectiveness to be evaluated when patients with stage IB disease are either included or excluded in the analysis. The base case ICER for the primary population is £5,292.

Further information on how the cost effectiveness analysis was conducted can be found in Appendix D.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	EGFR Positive UK Lung Cancer Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	EGFR Positive UK is a registered lung cancer charity supporting patients and families affected by EGFR mutation positive lung cancer. We provide information, share treatment experiences and support our members as well as campaigning for new treatments, earlier diagnosis and raising awareness of issues facing lung cancer patients. Currently, we have just under two hundred members from across the UK.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	NO

If so, please state the name of manufacturer, amount, and purpose of funding.	
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?	**Asking for information and experiences from members via our Facebook group**
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Currently, mutation testing is only available for patients with stage IV disease so the vast majority of our members were stage IV at diagnosis or have progressed to stage IV – in fact a recent membership survey revealed that 87% of members were diagnosed at stage IV. Living with stage IV disease is extremely difficult, despite the advances in treatments and the huge benefits of targeted therapies. Many of our members, due to the nature of EGFR mutation positive lung cancer, are younger, working, and still have dependent children. Psychologically, socially, and economically life can be extremely challenging. Once targeted therapies are no longer an option, chemotherapy or IMPower 150 remain the next line treatments with all the attendant issues in terms of

	increased hospital visits and admissions, side effects and the mental health implications for families and patients of dealing with progressive disease.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients benefit hugely from the targeted therapies available, many of which allow patients to live relatively normal day to day lives. However, there are fewer options once resistance to these TKIs develop. An adjuvant treatment for EGFR mutation positive lung cancer after complete tumour resection to prevent/delay progression would be welcomed by patients. In the experience of our members, osimertinib is a well- tolerated drug, with a low toxicity profile. It is our opinion that patients would be keen to have the choice of adding in this drug in this setting and it is important that this option is available for them.
8. Is there an unmet need for patients with this condition?	See above
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is an important option for patients in order to delay or prevent progression; in addition osimertinib is a well- tolerated drug with generally minimal side effects.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No**

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- It is our opinion that patients would welcome the option of adjuvant treatment which could delay/or prevent progression.
- Osimertinib is a well-tolerated with minimal side effects as experienced by our members.
- From a social and economic as well as a health/treatment perspective, an option which increases DFS has huge benefits.
-
-

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**The Royal College of Pathologists**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
9. How is the condition 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?	
10. 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 clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	There are well established pathways within histopathology departments throughout the UK for EGFR testing in NSCLC however there are differences with regards to inclusion criteria. Whilst some departments reflex test all NSCLC for EGFR irrespective of stage, others may only test specimens when requested to after discussion at MDT e.g. for high stage NSCLC only. If this technology was approved it will likely result

	in an increased demand for EGFR testing. Appropriate education and training of pathologists and funding for testing would need to be considered.
11. 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?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
15. Do you consider that the use of the technology will result in any substantial health-	

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• 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?	

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. 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?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA653, TA654]?	
21. How do data on real-world experience compare with the trial data?	
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23a. What proportion of people with NSCLC in the UK have mutations to the protein epidermal growth factor receptor (EGFR)?	Approximately 10-15%. There is less data available in the literature specifically related to the mutation rate in lower stage NSCLC.
23b. Do you expect osimertinib be given in addition to standard care, or do you expect it to replace some elements of standard care?	

23c. Would you expect treatment benefits to be different in people who received chemotherapy prior to osimertinib compared with those who did not?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- As stated in the scope, appropriate economic modelling is required because if this technology is approved it may result in an increased demand for EGFR testing and appropriate education and funding would need to be considered for cellular pathology departments.
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-
-
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Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection: A Single Technology Appraisal

Produced by	The School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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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.

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Katy Cooper and Katie Sworn summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Geoff Holmes and Jean Hamilton summarised and critiqued the statistical aspects of the submission. Paul Tappenden and Kate Ennis critiqued 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
AIC	Akaike Information Criterion
AFT	Accelerated failure time
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
AM	Active monitoring
ASA	Additional sensitivity analysis
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian Information Criterion
BNF	British National Formulary
CAA	Commercial Access Agreement
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CMU	Commercial Medicines Unit
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTX	Chemotherapy
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
EA	Exploratory analysis
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EGFRm	EGFR mutation
ELCC	European Lung Cancer Congress
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality of life questionnaire
EQ-5D-3L	Euroqol 5-Dimensions (3-level)
EQ-5D-5L	Euroqol 5-Dimensions (5-level)
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
FAD	Final appraisal determination
FAS	Full analysis set
GLS	Generalised least squares
GP	General Practitioner
HCHS	Hospital and Community Health Services
HIV	Human immunodeficiency virus
HODaR	Health Outcomes Data Repository
HR	Hazard ratio
HRQoL	Health-related quality of life

HTA	Health Technology Assessment
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
ICTRP	(WHO) International Clinical Trials Registry Platform
ILD	Interstitial Lung Disease
INAHTA	International Network of Agencies for Health Technology Assessment
IPD	Individual patient data
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
IV	Intravenous
LACE	Lung Adjuvant Cisplatin Evaluation
LRR	Loco-regional recurrence
LVEF	Left Ventricular Ejection Fraction
LYG	Life year gained
MCS	Mental component summary
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NACLC	North America Conference on Lung Cancer
NC	Not calculable
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NICE DSU	NICE Decision Support Unit
NMA	Network meta-analysis
NSCLC	Non-small-cell lung cancer
ONS	Office for National Statistics
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PDC	Platinum doublet chemotherapy (pemetrexed plus cisplatin)
PCS	Physical component summary
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
RCT	Randomised controlled trial
RDI	Relative dose intensity
RePEc	Research Papers in Economics
RMME	Repeated measures mixed effect
ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
SA	Scenario analysis
SAE	Serious adverse event
SD	Stable disease
SE	Standard error
SEER	US Surveillance Epidemiology and End Results
SF-36	36-Item Short Form Survey
SJS	Stevens-Johnson syndrome
SLR	Systematic literature review

SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SoC	Standard of care
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TP	Transition probability
TSD	Technical Support Document
TTD	Time to treatment discontinuation
UK	United Kingdom
US FDA	United States Food and Drug and Administration
WCLC	World Conference on Lung Cancer
WHO	World Health Organization
WTP	Willingness-to-pay

1 EXECUTIVE SUMMARY

1.1 Overview of the ERG's key issues

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs). Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

The company's submission (CS) includes a systematic literature review (SLR) and *de novo* health economic model of osimertinib as adjuvant treatment for people with epidermal growth factor receptor (EGFR) mutation-positive (EGFRm-positive) non-small-cell lung cancer (NSCLC) after complete tumour resection (with or without adjuvant chemotherapy). Osimertinib is a tyrosine kinase inhibitor (TKI) which targets EGFR sensitising mutations and inhibits the emergence of EGFR T790M resistance mutations. Osimertinib currently has a marketing authorisation for the first-line and second-line treatment of patients with locally advanced or metastatic EGFRm-positive NSCLC.

The key issues identified by the ERG are summarised in Table 1.

Table 1: Overview of the ERG's key issues

ID3835	Summary of issue	Report sections
Issue 1	Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS	Section 4.2.3
Issue 2	Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib	Section 5.3.4
Issue 3	Uncertainty surrounding the company's cure assumptions and OS predictions	Section 5.3.4
Issue 4	Uncertainty regarding re-treatment with osimertinib	Section 5.3.4
Issue 5	Limitations of available utility values for EGFRm-positive NSCLC	Section 5.3.4
Issue 6	Absence of subgroup analyses for patients with stage IB NSCLC	Section 5.3.4

DFS - disease-free survival; EGFRm-positive - epidermal growth factor receptor mutation-positive; ERG - Evidence Review Group; NSCLC - non-small-cell lung cancer; OS - overall survival

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the company's model suggests that adjuvant osimertinib affects QALYs by:

- Reducing the probability of experiencing loco-regional and distant recurrence, relative to active monitoring
- Extending overall survival (OS), both as a consequence of model-predicted disease-free survival (DFS) benefits and the incorporation of a structural cure assumption (applied to patients who are still disease-free at 5 years)
- Increasing health losses due to adverse events (AEs) associated with adjuvant treatment.

Overall, the company's model suggests that adjuvant osimertinib affects costs by:

- Increasing the costs of adjuvant treatment with osimertinib for patients who are disease-free
- Reducing downstream treatment costs, particularly those associated with osimertinib given as first-line treatment for patients with distant metastases
- Reducing the expected costs of treating loco-regional recurrence (by avoiding these events).

The modelling assumptions that have the greatest effect on the ICER are:

- The timepoint at which cure is assumed for patients who remain disease-free and whether this is applied equally to both treatment groups
- The parametric survival models used to predict the probability of transitioning from the disease-free (DF) health state to the loco-regional recurrence (LRR) and first-line distant metastases (DM1) health states
- The inclusion of other less expensive TKIs as first-line treatments for distant metastases within the active monitoring comparator group. Whilst osimertinib is not currently the only TKI used as first-line treatment for distant metastases, its use is expected to increase in the future, unless it is recommended in the adjuvant setting.

1.3 The decision problem: summary of the ERG's key issues

The ERG considers that the decision problem addressed in the CS is consistent with the final NICE scope, and that the clinical evidence presented in the CS is relevant to the decision problem. The target population in the CS is people with EGFRm-positive NSCLC after complete tumour resection (with or without adjuvant chemotherapy). The intervention in the CS is adjuvant osimertinib. The comparator in the CS is active monitoring without osimertinib. Clinically meaningful outcomes are presented in the

CS, including DFS, OS, sites and rates of recurrence, time to treatment discontinuation (TTD), AEs and health-related quality of life (HRQoL).

The ERG considers the company's description of the underlying health problem in the CS to be appropriate. The company's view of the treatment pathways with and without adjuvant osimertinib is shown in Figure 1 and Figure 2 of this report. The ERG believes that there are some uncertainties regarding the downstream treatment pathways for distant metastases presented in the CS and included in the company's economic model, both with and without adjuvant osimertinib. The ERG notes the following issues relating to the downstream treatments assumed in the model:

(i) All patients are assumed to receive active treatment for distant metastases, irrespective of patient fitness and choice
(ii) Re-treatment with osimertinib for distant metastases is assumed, yet personal communication received from NHS England (NHSE) indicates that this will not be permitted
(iii) The active monitoring group within the company's model does not include other TKIs (erlotinib, gefitinib, afatinib or dacomitinib) which are currently used for the first-line treatment of distant metastases
(iv) Neither treatment group includes the four-drug regimen of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) for the second-line treatment of distant metastases
(v) Personal communication from NHSE indicates that if adjuvant osimertinib was recommended, ABCP could be used as first-line treatment; this is not included in the company's model (although the ERG notes that EGFRm-positive patients enrolled in the pivotal IMPower150 trial had been previously treated)
(vi) Neither treatment group includes nintedanib plus docetaxel as second-line treatment for distant metastases.

These issues are discussed further in Section 1.5.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG considers that the clinical evidence presented in the CS is representative of clinical practice in England. The clinical effectiveness evidence for adjuvant osimertinib is based on the ADAURA randomised controlled trial (RCT) of adjuvant osimertinib versus placebo (active monitoring) for people with completely resected stage IB−IIIA EGFRm-positive NSCLC (some of whom also had adjuvant chemotherapy). The ADAURA trial is applicable to the decision problem and reports relevant outcomes.

The main uncertainty surrounding the clinical effectiveness of adjuvant osimertinib relates to the limited OS data available, as discussed below (Issue 1).

Issue 1: Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS

Report section	Section 4.2.3
Description of issue and why the ERG has identified it as important	The main issue relating to the ADAURA trial is the immaturity of the OS data. Treatment duration for adjuvant osimertinib in the ADAURA trial was planned for 3 years or until disease recurrence or fulfilment of discontinuation criteria. However, the trial was unblinded two years early due to overwhelming efficacy with osimertinib for DFS, and the data presented in the CS are based on this interim analysis. Median duration of treatment was 22.5 months in the osimertinib arm and 18.7 months in the placebo arm. There was a statistically significant DFS benefit for osimertinib, with hazard ratio (HR) and confidence interval (CI) as follows: HR 0.20 (99.12% CI 0.14, 0.30; p<0.001). However, OS data were immature, with only 9 deaths (2.7%) in the osimertinib arm and 20 deaths (5.8%) in the placebo arm; [redacted]. Therefore, it is uncertain whether the statistically significant DFS benefit will translate into a significant OS benefit.
What alternative approach has the ERG suggested?	The ERG has undertaken exploratory analyses which assess the impact of making optimistic and pessimistic assumptions regarding the timepoint at which the cure assumption is applied in the company's economic model. This has implications for predicted OS estimates and for the cost-effectiveness of adjuvant osimertinib. The impact of these alternative assumptions is detailed in Section 1.5.
What is the expected effect on the cost-effectiveness estimates?	The impact of alternative assumptions regarding the timing of cure is described in Section 1.5.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up of ADAURA may resolve some of the uncertainty around the OS benefits of adjuvant osimertinib.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The CS presents the methods and results of a *de novo* health economic model of osimertinib as adjuvant therapy versus active monitoring for patients with completely resected, stage IB-IIIA EGFRm-positive NSCLC. The model estimates the incremental cost-effectiveness of adjuvant osimertinib versus active monitoring over a lifetime horizon from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The model adopts a state transition (semi-Markov) approach and includes 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. The model uses time-to-event data from ADAURA to estimate the time-dependent risk of loco-regional and distant recurrence for patients who are disease-free. Other transitions for patients with loco-regional and distant recurrence, including those relating to mortality risk, are informed by external data, including the CancerLinQ database, the FLAURA trial (osimertinib versus erlotinib or gefitinib for first-line treatment of EGFRm-positive advanced NSCLC) and general population life tables from the Office for National Statistics (ONS). Patients who remain disease-free are assumed to have no

excess mortality risk. The model includes a key assumption whereby after 5 years, the predicted probabilities of relapse applied in the DF health state are reduced by 95% in both treatment groups. This increases the probability that patients remain disease-free and corresponds to a structural assumption of cure for most patients after this timepoint. The model also assumes that all patients who receive active monitoring who develop distant metastases would receive osimertinib in the first-line setting (in DM1). Overall, the model predicts that adjuvant osimertinib: (a) increases DFS (as observed in ADAURA); (b) extends OS (as a consequence of improved DFS and the structural cure assumption); (c) increases adjuvant treatment costs (due to the costs of adjuvant osimertinib), and (d) reduces downstream treatment costs (largely as a consequence of fewer patients requiring osimertinib in the metastatic setting).

The ERG identified a number of errors in the company's original submitted model. As part of their response to clarification questions from the ERG, the company submitted an updated model which resolved the majority of these errors and which included additional functionality to explore further scenarios. The probabilistic version of the company's updated model suggests that the ICER for adjuvant osimertinib versus active monitoring is £11,314 per QALY gained. The deterministic ICER is similar (£11,136 per QALY gained).

The key uncertainties relate to the company's cure assumptions and their impact on OS. The ERG's preferred analyses reflect two scenarios: (i) an optimistic scenario which retains the company's base case assumptions of cure, and (ii) a pessimistic scenario in which the cure timepoint for the adjuvant osimertinib group is applied after 8 years (i.e. 5 years plus the 3-year maximum adjuvant osimertinib treatment time). The latter scenario was undertaken to reflect a potential situation whereby osimertinib delays some relapses rather than preventing them altogether. The ERG's preferred optimistic ICER for adjuvant osimertinib is £9,838 per QALY gained. The ERG's preferred pessimistic ICER is £20,301 per QALY gained. Both of these estimates are based on the probabilistic version of the model.

The ERG's key issues relating to the cost-effectiveness evidence are summarised below. These are: uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib (Issue 2); uncertainty surrounding the company's cure assumptions and OS predictions (Issue 3); uncertainty regarding re-treatment with osimertinib (Issue 4); limitations of available utility values for EGFRm-positive NSCLC (Issue 5), and the absence of economic subgroup analyses for patients with stage IB NSCLC (Issue 6).

Issue 2: Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib

Report section	Section 5.3.4
Description of issue and why the ERG has identified it as important	The company's original and updated base case models assume that patients receiving active monitoring who develop distant metastases will receive first-line osimertinib followed by second-line platinum doublet chemotherapy (PDC; pemetrexed plus cisplatin). Within the intervention group, all patients who develop distant metastases within 5 years of starting adjuvant osimertinib treatment are assumed to receive PDC followed by docetaxel. After this 5-year timepoint, 50% of patients who develop distant metastases are assumed to be re-treated with osimertinib as first-line therapy followed by PDC, with the remaining 50% receiving PDC followed by docetaxel. The ERG has several concerns regarding this assumed treatment pathway: (i) All patients are assumed to receive active treatment, irrespective of patient fitness and choice (ii) Re-treatment with osimertinib is assumed, yet personal communication from NHSE indicates that this will not be permitted (iii) The active monitoring group does not include other TKIs (erlotinib, gefitinib, afatinib or dacomitinib) which are currently used as first-line treatments for distant metastases (iv) Neither treatment group includes the four-drug ABCP regimen for the second-line treatment of distant metastases. (v) Personal communication from NHSE indicates that if adjuvant osimertinib was recommended, ABCP could be used as first-line treatment (although the ERG notes that EGFRm-positive patients enrolled in the pivotal IMPower150 trial were previously treated). (vi) Neither treatment group includes nintedanib plus docetaxel as second-line treatment. The company's updated model allows for scenarios relating to issues (i) to (iv) to be assessed individually.
What alternative approach has the ERG suggested?	The ERG's preferred analyses include ABCP as a second-line treatment in both groups and exclude re-treatment in the adjuvant osimertinib group. The ERG notes that whilst other TKIs may be used for the first-line treatment of distant metastases, NICE has recently recommended osimertinib for metastatic disease and it is expected that the use of this drug will increase (subject to recommendations on adjuvant use and NHSE commissioning policies for TKIs). The company's clarification response and the ERG's exploratory analyses each include additional scenarios in which other TKIs are used. The ERG notes that if re-treatment is not permitted, the company's model assumes that a patient who receives adjuvant osimertinib and subsequently develops distant recurrence will go on to receive PDC followed by docetaxel. It is unclear whether this pathway is appropriate.
What is the expected effect on the cost-effectiveness estimates?	Including ABCP in the ERG's error-corrected model reduces the ICER from £10,795 to £9,900 per QALY gained. When other first-line TKIs are assumed, the ERG's preferred optimistic ICER is estimated to be £19,391 per QALY gained, whilst the ERG's preferred pessimistic ICER is estimated to be £33,330 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	The company has already provided data on the current use of TKIs for metastatic disease. It is expected that the use of osimertinib in the metastatic setting will increase in the future, although this will depend on whether osimertinib is recommended in the adjuvant setting.

Issue 3: Uncertainty surrounding company's cure assumptions and OS predictions

Report section	Section 5.3.4
Description of issue and why the ERG has identified it as important	The available OS data from ADAURA are limited. Despite this, the company's original model predicts a substantial incremental OS gain of [redacted] years for adjuvant osimertinib versus active monitoring. This predicted OS gain is a function of all transitions included in the model, most of which are informed by external data, and the company's structural cure assumption (model-predicted risks of transitioning from DF to LRR and DM1 are reduced by 95% from 5 years onwards). This cure assumption accounts for a substantial proportion of this predicted OS gain for adjuvant osimertinib (incremental OS gain excluding cure = [redacted] years). There is uncertainty surrounding the timing of the cure assumption under current practice (active monitoring) and whether adjuvant osimertinib will prevent, or only delay, disease recurrence beyond this timepoint. The ERG's clinical advisors considered that the company's modelled OS gains may be *"too generous"* and suggested that a more modest difference between the curves might be expected, especially if a greater proportion of the active monitoring group go on to receive osimertinib in the metastatic setting.
What alternative approach has the ERG suggested?	The ERG's preferred pessimistic analysis applies a later timepoint for cure in the adjuvant osimertinib group of 8 years (i.e. 5 years plus the 3-year maximum adjuvant osimertinib treatment time). A further additional sensitivity analysis was undertaken to explore the impact of applying less favourable parametric survival models for transitions out of the DF health state in the adjuvant osimertinib group (transition probability 1 [TP1]=log-logistic and TP2=log-normal); however, this is very pessimistic.
What is the expected effect on the cost-effectiveness estimates?	The ERG's preferred pessimistic scenario suggests a probabilistic ICER for adjuvant osimertinib of £20,301 per QALY gained. The ERG's highly pessimistic additional sensitivity analysis including alternative parametric survival models for TP1 and TP2 leads to a higher deterministic ICER of £54,913 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up of ADAURA may resolve some of the uncertainty surrounding the model predictions of incremental OS.

Issue 4: Uncertainty regarding re-treatment with osimertinib

Report section	Section 5.3.4
Description of issue and why the ERG has identified it as important	The company's model assumes that some patients who receive adjuvant osimertinib and subsequently develop distant metastases will go on to receive osimertinib as first-line treatment in the metastatic setting (50% of patients who enter the DM1 health state after 5 years). 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 ERG's clinical advisors indicated that re-treatment may be appropriate for patients whose disease did not recur whilst receiving adjuvant osimertinib or within a short time of completing adjuvant treatment. However, they also suggested that re-treatment with osimertinib would likely not be as effective as first-time use in the metastatic setting. Personal communication from NHSE received by the ERG indicates that based on the present evidence, the NHS would not allow further TKI use in a patient who progresses on or after osimertinib; hence re-treatment would not be permitted.
What alternative approach has the ERG suggested?	The ERG's preferred analyses exclude re-treatment with osimertinib. If re-treatment is permitted, it may be appropriate to consider further scenarios in which effectiveness is assumed to be lower than that observed in FLAURA.
What is the expected effect on the cost-effectiveness estimates?	The company's assumed timepoint for re-treatment coincides with the assumed timepoint for cure – this reduces the proportion of patients reaching DM1, thereby reducing the impact of including or excluding re-treatment on the ICER. Including re-treatment increases the ICERs for the ERG's optimistic scenario to £10,808 per QALY gained and for the ERG's pessimistic scenario to £22,989 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up from ADAURA may help to resolve uncertainty surrounding the plausibility of the company's cure assumptions and the modelled OS predictions. If re-treatment is not permitted, this is already captured in the ERG's preferred analyses. In addition, it would be useful to have data from ADAURA on which downstream treatments were received by patients in each arm who went on to experience distant metastases, and how many patients in each arm received osimertinib for distant metastases.

Issue 5: Limitations of available utility values for EGFRm-positive NSCLC

Report section	Section 5.3.4
Description of issue and why the ERG has identified it as important	Within the company's original model, health state utility values are based on Euroqol 5-Dimensions 3-level (EQ-5D-3L) estimates from ADAURA (mapped from the 36-Item Short Form [SF-36]), EQ-5D-3L estimates from FLAURA (mapped from the European Organisation for Research and Treatment of Cancer quality of life questionnaire [EORTC QLQ-C30]) and published EQ-5D-3L estimates from the literature (Labbé *et al*). Disutilities associated with AEs are based on published literature (Nafees *et al*, standard gamble) and NICE TA653 (elicitation/valuation method unclear). The ERG has three main concerns with the utility values applied in the company's original model: (i) The utility value applied in the DF and LRR health states (utility = [redacted]) is higher than that for the age- and sex-matched population (utility = 0.81). (ii) The utility value applied in the DM1 state (utility = 0.794) may be implausibly high (iii) The model does not include HRQoL decrements for potential late effects of adjuvant treatment or AEs associated with downstream treatments.
What alternative approach has the ERG suggested?	The company's updated model uses health utility estimates for the general population in the DF and LRR health states. Whilst this addresses the ERG's concerns to some degree, the updated model still assumes that patients do not experience any HRQoL decrement as a consequence of treatments previously received (surgery with/without adjuvant chemotherapy, as well as other treatments for loco-regional relapse, such as chemoradiation). The company's HRQoL SLR identified only one relevant alternative study which was included in the company's scenario analyses (Andreas *et al*.). Previous NICE Technology Appraisals (TAs) of treatments for metastatic EGFRm NSCLC have also assumed generally high utility values for patients who are free from disease progression. The ERG has conducted additional sensitivity analyses which use alternative utility values from Andreas *et al.* and which include longer-term QALY losses associated with AEs.
What is the expected effect on the cost-effectiveness estimates?	Including utility values from Andreas *et al.* increase the ERG's preferred optimistic and pessimistic ICERs to £10,467 and £21,032 per QALY gained, respectively. The ERG's additional scenario in which AE-related QALY losses apply for one year have a negligible impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Future utility valuation studies in patients with EGFRm NSCLC may provide more plausible estimates. The ERG is unaware of any alternative relevant sources which could be used to inform the health utility values in the model.

Issue 6: Absence of subgroup analyses for patients with stage IB NSCLC

Report section	Section 5.3.4
Description of issue and why the ERG has identified it as important	The final NICE scope states that *"If the evidence allows, subgroups based on NSCLC stage (IB versus II-IIIA) may be considered."* The company's economic model reflects the overall population of ADAURA. The CS does not report an economic subgroup analysis for patients with stage 1B NSCLC. The company's clarification response states that the available data are limited for the stage 1B subgroup ([redacted] and [redacted] events for osimertinib and placebo, respectively) and that the study was not powered to assess the efficacy of osimertinib by stage of disease. The company's clarification response includes a subgroup analysis for patients with stage II-IIIA NSCLC, which resulted in an ICER of £5,292 per QALY gained. This is lower than the ICER in the overall target population, which implies that osimertinib is likely to be less cost-effective in the stage 1B subgroup; however, this economic subgroup analysis has not been undertaken and the ICER in the stage 1B population is unknown.
What alternative approach has the ERG suggested?	The ERG would prefer to see an economic subgroup analysis for patients with stage 1B NSCLC; however, data are currently very limited.
What is the expected effect on the cost-effectiveness estimates?	The ICER for adjuvant osimertinib is likely to be higher in patients with stage 1B NSCLC compared with the overall target population.
What additional evidence or analyses might help to resolve this key issue?	Further follow-up of ADAURA may allow for a robust economic subgroup analysis to be performed for patients with stage 1B NSCLC.

1.6 Summary of ERG's preferred assumptions and resulting ICER

The results of the ERG's exploratory analyses (EAs) are summarised in Table 2. Each analysis reflects individual model amendments relative to the ERG-corrected version of the model (EA1). The ERG's preferred optimistic analysis (5-year cure timepoint in both groups) suggests that the ICER for adjuvant osimertinib versus active monitoring is £9,838 per QALY gained, based on the probabilistic version of the model. The ERG's preferred pessimistic analysis (8-year cure timepoint for adjuvant osimertinib group) is £20,301 per QALY gained. The ICERs generated using the deterministic version of the model are similar to their probabilistic counterparts.

Table 2: Summary of ERG preferred assumptions and ICERs

Scenario	Incremental QALYs	Incremental cost	ICER (change from company's updated base case)
Company's updated base case model (deterministic)	[redacted]	[redacted]	**£11,136**
EA1: Correction of remaining model errors	[redacted]	[redacted]	**£10,795** (-£341)
EA2: No re-treatment allowed for osimertinib	[redacted]	[redacted]	**£10,111** (-£1,025)
EA3: 5-year treatment effect for metastatic osimertinib DM1 to DM2	[redacted]	[redacted]	**£11,815** (+£679)
EA4: Update unit costs for administration of chemotherapy and docetaxel drug acquisition	[redacted]	[redacted]	**£10,742** (-£394)
EA5: Inclusion of wastage for osimertinib (0.50 packs)	[redacted]	[redacted]	**£10,657** (-£479)
EA6: Inclusion of ABCP treatment option	[redacted]	[redacted]	**£9,900** (-£1,236)
EA7: 8-year cure point applied	[redacted]	[redacted]	**£22,460** (+£11,324)
EA8: ERG preferred optimistic analysis (EA1-EA6 combined, probabilistic)	[redacted]	[redacted]	**£9,838** (-£1,298)
EA9: ERG preferred pessimistic analysis (EA1-EA7 combined, probabilistic)	[redacted]	[redacted]	**£20,301** (+£9,165)

EA - exploratory analysis; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel

The ERG's full critique of the company's economic analyses and the ERG's exploratory analyses can be found in the main ERG report (Sections 5.3 and 5.4, respectively).

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 (EGFRm-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, firstly for current treatment, and secondly with the addition of adjuvant osimertinib.

2.1 Critique of the company's description of the underlying health problem

The ERG considers that the description of the health problem presented in the company's submission (CS)[1] is broadly accurate. This is summarised below.

2.1.1 Prevalence and epidemiology

The CS[1] (Section B.1.3.1, page 19) states that NSCLC accounts for 80–89% of all lung cancers, with an estimated annual incidence in England of 36,875 patients.[2, 3] The CS states that EGFR mutations are found in approximately 10% of patients with NSCLC adenocarcinoma.[4] The total annual incidence of patients in England and Wales with EGFRm-positive NSCLC who are stage IB−IIIA, have undergone complete surgical resection, and who are eligible for adjuvant therapy is estimated in the CS to be 386, reaching a total of 485 incident patients after 5 years. The basis for these estimates is not presented in the CS. The company's fact check response[5] clarifies that these estimates are based on the company's budget impact analysis.

2.1.2 Prognosis

The CS[1] (Section B.1.3.1, page 19) states that approximately 18% of NSCLC patients in England and Wales undergo complete surgical resection with curative intent.[2] Despite complete resection, many patients experience disease recurrence within 5 years of surgery (45% with stage IB, 62% with stage II, and 76% with stage III disease), with 5-year mortality rates of 38-70% for stage IB-III NSCLC.[6] Most post-resection relapses are due to distant recurrence (particularly brain metastases). The CS states that disease recurrence most frequently occurs 18–24 months after surgery, based on interviews conducted with six UK clinicians by the company.[7] The CS (Section B.1.3.2, page 20) states that patients with EGFRm-positive NSCLC have twice the risk of brain metastases compared with patients with wild-type EGFR.[8]

2.1.3 Burden of disease

The CS[1] (Section B.1.3.2, page 20) highlights that early-stage NSCLC is often asymptomatic for many years. When symptoms arise, they may include shortness of breath, fatigue and nausea.[9] Among patients

with EGFRm NSCLC and brain metastases, ≥10% experience seizures, speech problems, focal neurologic deficits, drowsiness, and memory problems.[10] The CS (Section B.1.3.2, page 21) states that patients with NSCLC experience poorer physical health and poorer health-related quality of life (HRQoL) than the general population, with disease recurrence and progression leading to the largest decreases in HRQoL.[11, 12] Surgery and adjuvant chemotherapy are stated to cause temporary declines in HRQoL.[12, 13] Central nervous system (CNS) metastases, including brain metastases, cause greater decreases in HRQoL than non-CNS metastases.[7] The CS[1] also describes the economic burden of the disease, including absence from work 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).[14]

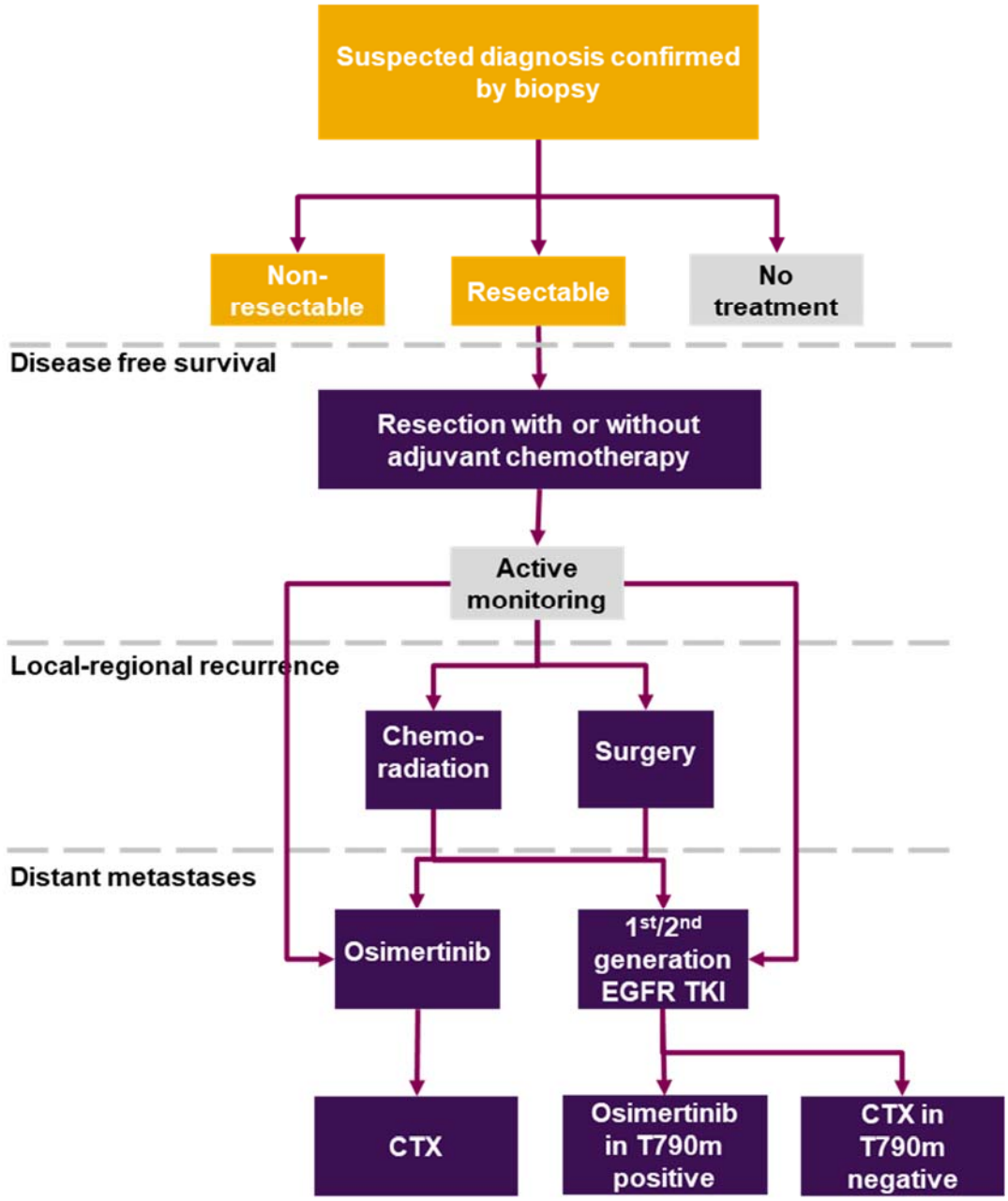
2.2 Critique of the company's overview of current service provision

2.2.1 Company's view of current pathway and proposed positioning of adjuvant osimertinib

The company's current care pathway is described in Section B.1.3.4 of the CS[1] and is illustrated in Figure 1. The company's anticipated pathway with the addition of adjuvant osimertinib is described in Section B.1.3.4.4 of the CS[1] and is illustrated in Figure 2.

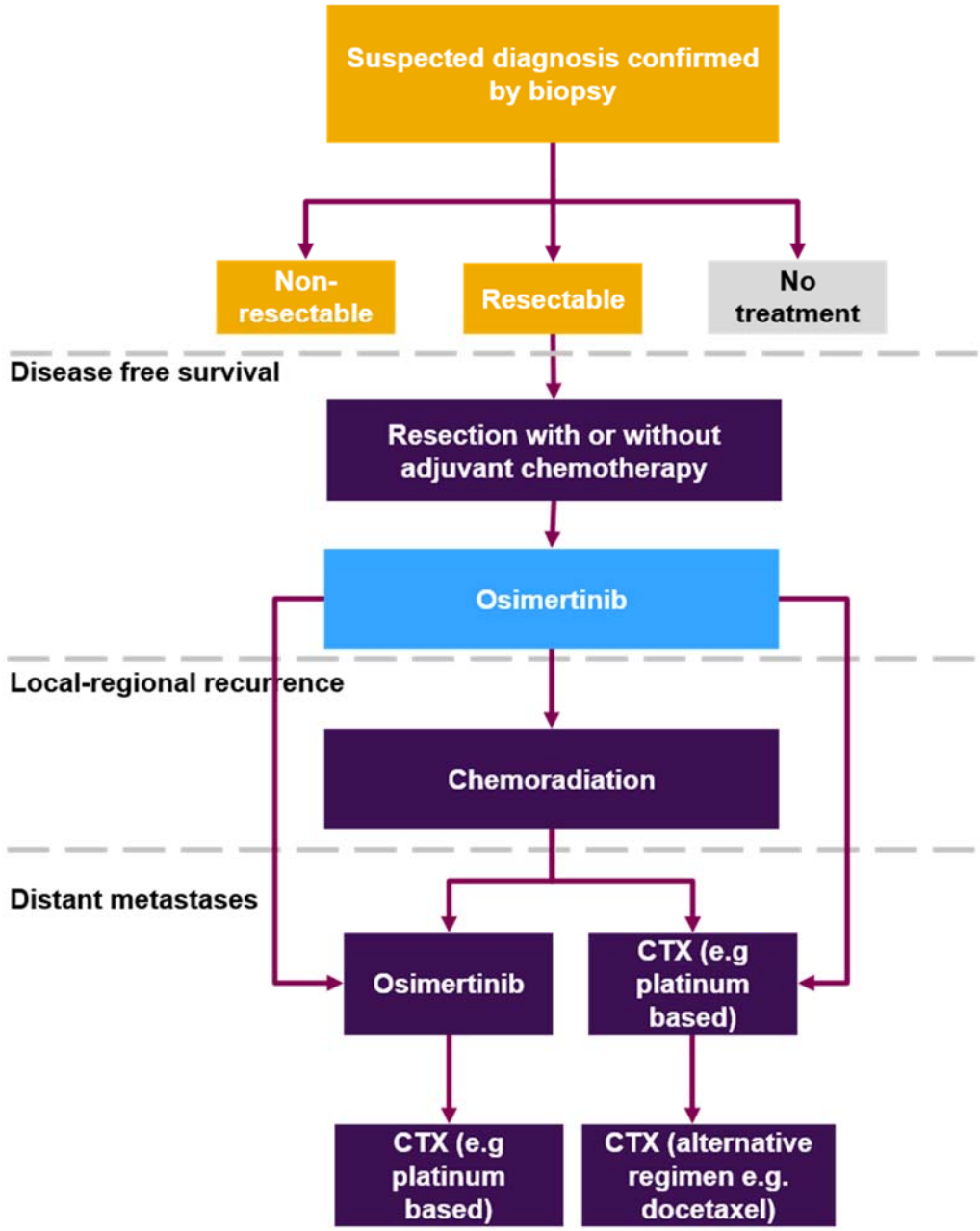
Osimertinib is a tyrosine kinase inhibitor (TKI) which targets EGFR sensitising mutations and inhibits the emergence of EGFR T790M resistance mutations. Osimertinib currently has a marketing authorisation for the first-line and second-line treatment of patients with locally advanced or metastatic EGFRm-positive NSCLC.[15] This appraisal addresses the use of osimertinib earlier in the pathway as an adjuvant treatment for people with EGFRm-positive NSCLC following complete tumour resection (with or without adjuvant chemotherapy).

Figure 1: Current pathway of care in resectable EGFRm-positive NSCLC (reproduced from CS, Figure 3)



Abbreviations: CTX - chemotherapy; EGFRm - epidermal growth factor receptor mutation; EGFR TKI - epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC - non-small cell lung cancer
Source: AstraZeneca UK clinician interviews; NICE Guideline 122.

Figure 2: Proposed positioning of osimertinib in resectable EGFRm-positive NSCLC (reproduced from CS, Figure 4)



CS footnotes: The proposed positioning of osimertinib in this submission is shown in blue. The treatment pathway shown here is consistent with that presented in the economic model (CS Section B.3.). Surgery for loco-regional recurrence is not shown due to the very small proportion of patients expected to be treated with this in clinical practice.
Abbreviations: CTX - chemotherapy; EGFRm - epidermal growth factor receptor mutation; EGFR TKI - epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC - non-small cell lung cancer.
Source: AstraZeneca UK clinician interviews.

2.2.2 Summary of ERG's critique of company view of current and future treatment pathways

A brief summary of the ERG's critique of the company's description of the current and future treatment pathway (if adjuvant osimertinib is recommended) is provided below. The subsequent sections provide a more in-depth description and critique of these pathways.

With respect to the company's view of the current treatment pathway (Figure 1), the ERG notes the following observations:

- Loco-regional recurrence: Single-modality radiotherapy should be included as an option. The company's clarification response[16] (question A3) states that up to 18% of patients receive radiotherapy.
- Distant metastases, first-line treatment: The company's pathway diagram appears to be appropriate. However, the ERG notes that this view of the current pathway differs from the treatment pathway assumed in the company's health economic model, as the model assumes that all patients receive osimertinib and not other TKIs (see Sections 2.2.5 and 5.2).
- Distant metastases, second- and subsequent-line treatment: The pathway should include the four-drug regimen of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP; as assessed in NICE Technology Appraisal [TA] Number 584).[17] The company's clarification response[16] (question A4) states that up to 16% of patients may receive ABCP for the second-line treatment of distant metastases.

With respect to the company's pathway with adjuvant osimertinib (Figure 2), the ERG notes the following observations:

- Loco-regional recurrence: Single-modality radiotherapy should be included as an option. As described above, the company's clarification response[16] (question A3) states that up to 18% of patients receive radiotherapy.
- Distant metastases, first-line re-treatment with osimertinib: The company's proposed pathway assumes that some patients are re-treated with osimertinib; however, the CS[1] (page 28) notes that there are no clinical studies assessing re-treatment. Personal communication from NHSE received by the ERG indicates that based on the present evidence, the NHS would not allow further TKI use in a patient who progresses on or after osimertinib (hence, re-treatment would not be permitted).
- Distant metastases, other first-line treatments: For patients who are not re-treated with osimertinib, clinical advisors to the ERG suggested that standard treatment would be ABCP in patients with no contraindications to any element of this regimen. Whilst ABCP is not recommended for the first-line treatment of patients with EGFRm-positive NSCLC according to NICE TA584,[17] personal communication from NHSE indicated that if osimertinib is commissioned in the adjuvant setting, NHSE would commission ABCP as the next line of therapy. However, within the pivotal IMPower150 trial of ABCP in NSCLC,[18] EGFRm-positive patients were only included if they had previously failed on a TKI and therefore were receiving ABCP as second-line treatment for metastatic disease. For patients who are frail or

have contraindications to ABCP, the ERG's clinical advisors stated that standard care would be platinum doublet chemotherapy (PDC; pemetrexed plus cisplatin).

- Distant metastases, second- and subsequent-line: Treatment following osimertinib should include ABCP.[17] The company's clarification response[16] (question A4) states that up to 16% of patients may receive ABCP for second-line treatment of distant metastases. Alternative chemotherapy following initial chemotherapy should include docetaxel with or without nintedanib (TA347).[19, 20]

2.2.3 Description and ERG critique of company's view of the current care pathway

The following section outlines the company's current care pathway in more detail (Figure 1). The ERG's critique is integrated into this description.

Adjuvant treatment (current pathway)

The CS[1] (Section B.1, page 12) states that approximately 33% of UK patients with completely resected NSCLC receive adjuvant chemotherapy (ranging from 13% of stage IB to 50% of stage IIIA). According to the CS (Section B.1.3.4.2, page 26), post-operative cisplatin-based chemotherapy should be offered to all patients with good performance status (PS), i.e. World Health Organization (WHO) PS of 0 or 1, and either lymph node involvement or large (≥4 cm) primary tumours. The ERG agrees that this is consistent with the 2019 NICE guideline on the diagnosis and management of lung cancer (NG122).[21]

The CS[1] (Section B.1.3, page 18) states that adjuvant chemotherapy provides an absolute benefit of 5.4% for overall survival (OS) and 5.8% for disease-free survival (DFS) over 5 years compared with no chemotherapy, based on a pooled analysis of five trials of cisplatin-based chemotherapy for NSCLC (Lung Adjuvant Cisplatin Evaluation; LACE).[6] Clinical advisors to the ERG agreed that this is a relevant source and that the estimates are relevant, but noted that the data do not relate specifically to patients with EGFRm-positive NSCLC.

The CS[1] (Section B.1.3, page 18) states that following complete resection (with or without adjuvant chemotherapy), no further treatment options exist and patients undergo routine surveillance (also referred to as "active monitoring"), typically for 5 years. The final NICE scope,[22] NG122[21] and clinical advisors to the ERG all suggest that some patients may also receive adjuvant radiotherapy, which is not included in the company's pathway. However, the company's clarification response[16] (question A2) states that adjuvant radiotherapy would only be used for patients with incomplete resection; clinical advisors to the ERG agreed with this, hence the ERG agrees that adjuvant radiotherapy is not relevant to the target population who would be eligible for treatment with adjuvant osimertinib.

Other adjuvant EGFR TKIs

Previous trials have assessed the adjuvant use of first-generation EGFR TKIs such as gefitinib and erlotinib; however, none of these treatments have been the subject of NICE TAs in the adjuvant setting.[23-27] The CS[1] (Section B.1, page 12 and B.1.3, page 19) states that these trials showed no long-term DFS or OS benefit: the CS suggests that this may be partly due to poor blood-brain barrier penetration, limitations of the design of the trials which restricted treatment duration to 2 years, the inclusion of patients without negative margins after surgery, and trial populations that included patients with wild-type EGFR. The ERG notes that all the adjuvant TKI trials referenced in the CS[23-27] either restricted inclusion to EGFRm-positive patients or reported subgroup analyses for these patients, and that some previous trials (e.g. the EVAN trial[27] of erlotinib and the ADJUVANT/CTONG1104 trial[28] of gefitinib) compared the TKI against chemotherapy rather than against placebo, which may have reduced the expected treatment effect. Previous trials of adjuvant TKIs identified by the company's literature search are summarised in Section 4.1.7. Currently in England, EGFR TKIs are not used in the adjuvant setting for EGFRm-positive NSCLC.

Loco-regional recurrence (current pathway)

The company's current care pathway (Figure 1) indicates that patients with loco-regional recurrence may receive either chemoradiation or surgery. The clinical advisors to the ERG agreed that some patients receive chemoradiation and a very small proportion of patients receive surgery. In addition, the clinical advisors to the ERG suggest that some patients with loco-regional recurrence receive single modality radiotherapy; this is not included in the company's current pathway. The company's clarification response[16] (question A3) states that, according to their clinical advisors, the vast majority of patients receive chemoradiation while up to 18% of patients receive single-modality radiotherapy. Clinical advisors to the ERG suggested that the percentage receiving single-modality radiotherapy may be higher in NHS clinical practice.

Distant metastases, first-line treatment (current pathway)

The company's current care pathway (Figure 1) indicates that first-line treatment for distant metastases would be either osimertinib or other (first- or second-generation) EGFR TKIs. The ERG agrees that this is consistent with the NG122[21] as well as previous NICE TAs, which suggest that patients could receive either osimertinib (TA654[29]), gefitinib (TA192[30]), erlotinib (TA258[31]), afatinib (TA310[32]) or dacomitinib (TA595[33]). The CS[1] (Section B.1.3.4., page 27) states that UK clinicians described osimertinib as the current standard of care in the first-line metastatic setting. However, the clinical advisors to the ERG commented that both osimertinib and other EGFR TKIs are currently used in UK practice as first-line therapy for metastatic disease. Clinical advisors to the ERG further noted that, of the first- and second-generation EGFR TKIs, the most commonly used in NHS clinical practice are afatinib and gefitinib.

Distant metastases, second- and subsequent-line (current pathway)

The company's current care pathway (Figure 1) indicates that patients progressing after other first-line EGFR TKIs would receive osimertinib if they develop an EGFR T790M resistance mutation. The ERG agrees that this is consistent with the NICE lung cancer guideline (NG122[21]) and the previous NICE TA for second-line osimertinib (TA653[34]).

The company's pathway indicates that patients progressing after first-line osimertinib, as well as those progressing after other EGFR TKIs who are T790M-negative, would receive chemotherapy. However, clinical advisors to the ERG, as well as the NICE 2020 lung cancer algorithm[19] and NICE TA584,[17] suggest that the standard of care for second-line treatment of distant metastases is ABCP in patients with no contraindications; this regimen is not included in the company's current pathway. The company's clarification response[16] (question A4) states that up to 16% of patients may receive ABCP for second-line treatment of distant metastases. For patients who are frail or have contraindications to this regimen, standard care would be PDC.

2.2.4 Description and ERG critique of company's view of the treatment pathway with adjuvant osimertinib

This section outlines the company's anticipated pathway with the addition of adjuvant osimertinib (Figure 2). The ERG's critique is integrated into this description.

Adjuvant treatment (pathway with adjuvant osimertinib)

The ERG's comments on Figure 2 regarding adjuvant treatment are the same as for Figure 1. The ERG agrees that both pathways reflect clinical practice. Patients in Figure 2 would then receive adjuvant osimertinib (following adjuvant chemotherapy, if received). This would require EGFRm testing (CS,[1] page 27).

Loco-regional recurrence (pathway with adjuvant osimertinib)

The ERG's comments on Figure 2 regarding loco-regional recurrence are similar to those for Figure 1. The ERG agrees with the inclusion of chemoradiation for loco-regional recurrence in both pathways. The footnotes to Figure 2 state that *"Surgery for locoregional recurrence is not shown due to the very small proportion of patients expected to be treated with this in clinical practice."* The ERG's clinical advisors agreed with this statement. As with Figure 1, the ERG queried why Figure 2 does not include single-modality radiotherapy for loco-regional recurrence. The company's clarification response[16] (question A3) states that, according to their clinical advisors, the vast majority of patients receive chemoradiation, while up to 18% of patients receive single-modality radiotherapy. As noted above, clinical advisors to the ERG suggested that the percentage of patients receiving single-modality radiotherapy may be higher in NHS clinical practice.

Distant metastases, first-line: re-treatment with osimertinib (pathway with adjuvant osimertinib)

The company's pathway with adjuvant osimertinib (Figure 2) indicates that, at first-line treatment for distant metastases, some patients would be re-treated with osimertinib. This is discussed in the CS[1] (Section B.1.3.4.4., page 28), which states that there are no clinical studies assessing osimertinib in patients who have previously received it, and that the proportion of patients who would be re-treated is therefore uncertain. Personal communication from NHSE received by the ERG indicates that based on the present evidence, the NHS would not allow further TKI use in a patient who progresses on or after osimertinib; hence, re-treatment with osimertinib would not be permitted. The ERG's clinical advisors stated that it if re-treatment was permitted, this may be appropriate for patients whose disease did not recur whilst receiving adjuvant osimertinib or within a short time of completing adjuvant treatment; however, they also commented that there are no clinical studies assessing re-treatment. The clinical advisors further noted that patients would need to be re-biopsied and re-tested for EGFR mutation status and that re-treatment with osimertinib would likely not be as effective as first-time use in the metastatic setting, based on general findings regarding re-treatment with other cancer drugs. The ERG notes that the company's base case model assumes that 50% of patients developing distant metastases after initiating adjuvant osimertinib would be re-treated, and that the effectiveness of osimertinib in the metastatic setting is independent of whether the patient has previously received osimertinib as adjuvant treatment.

Distant metastases, other first-line treatments (pathway with adjuvant osimertinib)

Patients who are not re-treated with osimertinib are assumed to receive chemotherapy. Other EGFR TKIs are not listed as treatment options. The CS[1] (Section B.1.3.4.4, page 28) states that clinicians would not give other EGFR TKIs after adjuvant osimertinib because they are generally considered to be less potent and less efficacious than osimertinib. The ERG's clinical advisors agreed with this view.

In terms of chemotherapy treatment for first-line metastases, the ERG's clinical advisors considered that standard treatment would be ABCP (TA584[17]) in patients without contraindications, which is not currently included in the company's pathway (Figure 2). Whilst ABCP is not recommended for the first-line treatment of patients with EGFRm-positive NSCLC according to TA584,[17] personal communication from NHSE indicated that if osimertinib is commissioned in the adjuvant setting, NHSE would commission ABCP as the next line of therapy. However, within the pivotal IMPower150 trial of ABCP in NSCLC,[18] EGFRm-positive patients were only included if they had previously failed on a TKI and therefore were receiving ABCP as second-line treatment for metastatic disease. For patients who are frail or have contraindications to ABCP, the ERG's clinical advisors stated that standard care would be PDC.

Distant metastases, second- and subsequent-line (pathway with adjuvant osimertinib)

The company's pathway with adjuvant osimertinib (Figure 2) indicates that patients who progress after osimertinib (given first-line for distant metastases) would receive chemotherapy. As for the current care pathway, the ERG's clinical advisors suggest that standard of care would be ABCP (TA584[17]), which is not currently included in the company's pathway. The company's clarification response[16] (question A4) states that up to 16% of patients may receive ABCP for second-line treatment of distant metastases.

Patients progressing after first-line chemotherapy are stated to receive alternative chemotherapy such as docetaxel (Figure 2). Clinical advisors to the ERG, as well as NICE TA347[20] and the NICE (2020) lung cancer algorithm,[19] suggest that this should be docetaxel with or without nintedanib.

2.2.5 Assumed pathways included in the company's economic model

The ERG notes that the company's original health economic model does not fully reflect the pathways described in Figure 1 and Figure 2. Some of these discrepancies were addressed within an updated version of the model which was provided following the clarification round:[16]

- The company's original model assumed that all patients with loco-regional recurrence are treated with chemoradiation. The company's updated model includes single-modality radiotherapy for 18% of patients with loco-regional recurrence.
- The company's original model assumed that all patients who receive active monitoring and subsequently develop distant metastases are treated with first-line osimertinib followed by second-line PDC. Other TKIs were not included as either first- or second-line treatments. The company's clarification response[16] (question B2) presents a scenario analyses in which [redacted] of this group receive other TKIs for the first-line treatment of distant metastases.
- Other chemotherapy options such as ABCP were initially not considered in the second-line position. The company's clarification response[16] (question A4) presents a scenario analyses in which 16% receive ABCP as second-line treatment of distant metastases.
- The company's original model assumed that some patients who receive adjuvant osimertinib receive re-treatment with osimertinib as first-line treatment for distant metastases, followed by second-line PDC; those who are not re-treated with osimertinib are assumed to receive first-line PDC followed by docetaxel. Other chemotherapy options such as ABCP were not considered as first- or second-line treatments, whilst nintedanib plus docetaxel is not considered as a second-line treatment. The company's scenario analysis described in the previous bulletpoint assumes that 16% of patients who progress after re-treatment with osimertinib receive ABCP as second-line treatment.

The company's original and updated models are described in Section 5.2 and Section 5.3.5, respectively.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[22] and addressed in the CS is presented in Table 3, together with brief comments from the ERG. The ERG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: The decision problem (reproduced from CS, Table 1, with comments from the ERG)

	Final scope[22] issued by NICE	Decision problem addressed in the CS[1]	Rationale if different	ERG comments
Population	People with EGFR mutation-positive NSCLC after complete tumour resection (with or without adjuvant chemotherapy)	As per scope	N/a	Consistent with scope.
Intervention	Osimertinib (as an adjuvant treatment)	As per scope	N/a	Consistent with scope; however, osimertinib treatment duration is not specified in the CS[1] (see Section 3.2).
Comparator(s)	Established clinical management without osimertinib (that is, active monitoring)	As per scope	N/a	Consistent with scope.
Outcomes	The outcome measures to be considered include: • OS • DFS • Sites and rates of recurrence • TTD • AEs from treatment • HRQoL	As per scope	N/a	Consistent with scope.
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	The economic base case is based on the NICE Reference Case. A confidential commercial arrangement, including a Patient Access Scheme (PAS) is applicable for osimertinib for treating EGFR T790M mutation-positive advanced NSCLC (TA653) and osimertinib for untreated EGFR mutation-positive NSCLC (TA654). [redacted]	N/a	Consistent with scope

	Final scope[22] issued by NICE	Decision problem addressed in the CS[1]	Rationale if different	ERG comments
	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 5.9 of the Guide to the Methods of Technology Appraisals.	[redacted]		
Subgroups to be considered	If the evidence allows, subgroups based on NSCLC stage (IB versus II-IIIA) may be considered.	Pre-specified subgroups were included in the pivotal trial (ADAURA) and the relevant efficacy data are presented in this submission. These subgroups were based on demographics, cancer staging, EGFR mutation, and adjuvant chemotherapy. 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.	N/a	The ERG requested a subgroup analysis to assess the cost-effectiveness of osimertinib for patients with stage 1B disease; however, the company did not present this analysis as data are currently very limited (see Section 3.6)
Special considerations including issues related to equity or equality	-	N/a	N/a	N/a

Abbreviations: AE - adverse event; CAA - Commercial Access Agreement; CNS - central nervous system; DFS - disease-free survival; EGFR - epidermal growth factor receptor; HRQoL - health-related quality of life; N/a - not applicable; NHS - National Health Service; NSCLC - non-small cell lung cancer; OS – overall survival; PAS - Patient Access Scheme; TTD - time to treatment discontinuation

3.1 Population

Decision problem: The CS[1] (Table 1, page 14) states that the population consists of people with EGFRm-positive NSCLC after complete tumour resection (with or without adjuvant chemotherapy). The ERG agrees that this is consistent with the final NICE scope.[22]

Relevance of clinical evidence: The clinical data presented in the CS[1] is based on the ADAURA trial of adjuvant osimertinib versus placebo.[35] The CS (Section B.2.2, page 34) states that ADAURA included adults with 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 adjuvant chemotherapy. The ERG considers that the population of the ADAURA trial is broadly consistent with the decision problem, but notes that the trial population may be slightly fitter than that expected in NHS clinical practice (restricted to WHO PS 0-1, more females [redacted]). This issue is discussed further in Section 4.2.

3.2 Intervention

Decision problem: The CS[1] (Table 1, page 14) states that the intervention is osimertinib (Tagrisso®) given as an adjuvant treatment. This is consistent with the final NICE scope.[22] The wording of the anticipated licence indication for adjuvant osimertinib set out in the draft Summary of Product Characteristics (SmPC)[36] relates to: [redacted]

The CS[1] (Section B.1, page 11 and Section B.1.2, page 16, Table 2) states that osimertinib is an oral, CNS-active TKI that targets EGFR sensitising mutations and inhibits the emergence of EGFR T790M resistance mutations while having minimal impact against wild-type EGFR. The CS also states that EGFR mutation status should be confirmed in tumour or plasma specimens using a validated method of testing. Osimertinib currently has a marketing authorisation from the European Medicines Agency (EMA) for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations, and for adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC after first-line treatment with another EGFR-TKI. The CS (Section B.1.2, page 16, Table 2) states that the recommended daily dose of osimertinib is 80mg. The list price for 30 x 80mg tablets is £5,770. The company has a commercial arrangement that makes osimertinib available to the NHS with a discount [redacted]

The ERG notes that osimertinib treatment duration is not specified within the decision problem in the CS.[1] The draft SmPC[36] (page 5) states: [redacted]

Relevance of clinical evidence: The ERG considers that the intervention in the ADAURA trial[35] is consistent with the decision problem. The CS[1] (Section B.1.2, Table 2, page 16) states that the intervention group in ADAURA received osimertinib 80mg once daily for 3 years or until disease recurrence or fulfilment of a criterion for treatment discontinuation. However, the ERG notes that osimertinib treatment duration is not specified in the decision problem in the CS. The company's model includes a stopping rule whereby maximum treatment duration is assumed to be 3 years in the adjuvant setting.

Warnings and precautions for use of osimertinib: The draft SmPC[36] lists the following warnings and precautions for use of osimertinib:

[redacted]

[redacted]

3.3 Comparators

Decision problem: The CS[1] (Table 1, page 14) states that the comparator is established clinical management without osimertinib (active monitoring i.e. routine imaging and follow-up). The ERG considers that this is consistent with the final NICE scope.[22]

Relevance of clinical evidence: The ERG considers that the comparator in ADAURA[37] is consistent with the decision problem. The CS[1] (Section B.1.2, Table 2, page 16) states that the control group in ADAURA received placebo for 3 years or until disease recurrence or fulfilment of a criterion for treatment discontinuation.

3.4 Outcomes

Decision problem: The CS[1] (Table 1, page 14) states that the outcome measures to be considered include OS; DFS; sites and rates of recurrence; time to treatment discontinuation (TTD); adverse events (AEs) of treatment; and HRQoL. This is consistent with the final NICE scope.[22]

Relevance of clinical evidence: The ERG notes that the outcome measures listed in the decision problem are reported in the CS[1] for the ADAURA trial.[35] All outcomes except for TTD are reported in the clinical effectiveness section of the CS. The company's economic model includes data on DFS, site of recurrence, TTD, AEs and HRQoL from the ADAURA trial. Mortality risks for specific health states are modelled using external data from the FLAURA trial[38, 39] (osimertinib versus erlotinib or gefitinib for first-line treatment of EGFRm-positive advanced NSCLC) and general population life tables.[40]

3.5 Economic analysis

The CS[1] reports the methods and results of a model-based health economic analysis which estimates the incremental cost-effectiveness of adjuvant osimertinib versus active monitoring from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. Further details of the company's economic analyses are presented in Chapter 5.

3.6 Subgroups

Decision problem: Efficacy data for pre-specified subgroups for the ADAURA trial,[35] based on demographics, cancer staging, EGFR mutation, and adjuvant chemotherapy are presented in Section B.2.6.1 of the CS.[1] However, the CS states that no economic subgroup analyses are presented because a consistent treatment effect was observed, and therefore the analysis is based on the full trial population.

The ERG agrees that all subgroup analyses for DFS show a statistically significant effect of adjuvant osimertinib (CS,[1] Figure 9, page 51). However, the ERG notes that the magnitude of the DFS benefit for stage IB patients is smaller than that for patients with other disease stages. Therefore, during the clarification process, the ERG requested a subgroup analysis to assess the cost-effectiveness of osimertinib for patients with stage 1B disease. The company's clarification response[16] (question C3) states that this subgroup analysis was not undertaken, noting that the data in patients with stage IB disease are highly immature and that the study was not powered to assess efficacy by stage. However, as the study was powered to evaluate the efficacy of patients with stage II−IIIA disease, the company provided a subgroup analysis to assess the cost-effectiveness of osimertinib in patients with stage II−IIIA disease (clarification response, question C3). The requested analysis for the stage 1B subgroup was not presented. This issue is discussed further in Section 5.3.4.

4 CLINICAL EFFECTIVENESS

This chapter provides a summary and critique of the clinical evidence provided by the company addressing osimertinib for the adjuvant treatment of EGFRm-positive NSCLC after complete tumour resection. The clinical evidence submitted by the company consists of a systematic literature review (SLR) and a summary of evidence from the relevant clinical trial (ADAURA[37]). Section 4.1 summarises and critiques the methods of the company's SLR. Section 4.2 summarises and critiques the ADAURA trial. Section 4.3 briefly confirms that no indirect comparison was performed. Section 4.4. briefly confirms that no additional work relating to clinical effectiveness was performed by the ERG. Section 4.5 provides the ERG's conclusions regarding clinical effectiveness evidence for adjuvant osimertinib.

4.1 Critique of the methods of review

The CS[1] (Section B.2.1, page 33) and CS Appendix D[36] (Section D.1, page 10) 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 CS states that the search strategies used in the SLR were broad and were intended to inform a number of workstreams. However, only studies of adjuvant treatment in the EGFRm-positive population are considered in CS Appendix D, while only studies relating to the adjuvant use of osimertinib are included in the main CS.

4.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical effectiveness and safety studies of adjuvant therapies or comparator treatments of patients who have stage IB-IIIA NSCLC.

The company searched several electronic bibliographic databases in July 2020 (CS Appendix D[36]): MEDLINE [via Ovid]; MEDLINE in Process [via Ovid]; EMBASE [via Ovid]; the Cochrane Database of Systematic Reviews [via Wiley]; the Cochrane Central Register of Controlled Trials [via Wiley] and the Database of Abstracts of Reviews of Effects [via the Centre for Reviews and Dissemination; CRD].

The company also searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) in August 2020. Two regulatory sources, the EMA and the FDA, were also searched in August 2020. A relevant trials registry, the WHO International Clinical Trials Registry Platform (ICTRP) was searched in August 2020. The company searched several key conference abstract websites in the last three years (July 2018-July 2020): American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), ESMO European Lung Cancer Congress (ELCC), International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC) and North America Conference on Lung Cancer (NACLC).

The search strategies used by the company in both databases and grey literature (WHO ICTRP, EMA, FDA, ASCO, ESMO, ELCC, IASLC, NACLC) were clearly and fully reported and were reproducible. A comprehensive and multifaceted search strategy comprising the disease/EGFR/PD-1 terms was combined with the randomised controlled trial (RCT) and non-RCT design search filters and this was translated consistently across the databases. Having reviewed the search strategies, there were no consequential errors and the ERG considers that the search is comprehensive.

4.1.2 Inclusion criteria for the SLR

CS Appendix D[36] (page 22) states that abstracts and full texts were assessed for inclusion by two reviewers, which the ERG considers to be good practice. CS Appendix D (Table 8, page 23) states that the broad systematic review of adjuvant therapies for EGFRm-positive NSCLC used the following inclusion criteria:

- Population: Patients with EGFRm-positive stage IB–IIIA NSCLC following complete tumour resection
- Intervention: Any adjuvant treatment for stage IB–IIIA NSCLC following complete tumour resection
- Comparators: Any or none
- Outcomes: Includes all those listed in decision problem
- Study design: 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.

Of the studies identified using the above criteria, only adjuvant studies of osimertinib are included in the main CS.[1]

4.1.3 Inclusion criteria for the indirect comparison

No indirect comparison was conducted.

4.1.4 Critique of data extraction

CS Appendix D[36] (page 24) states that data were extracted by one reviewer and verified by a second reviewer. The ERG considers this to be good practice.

4.1.5 Quality assessment

CS Appendix D[36] (page 24) states that the quality of RCTs (including ADAURA[35]) was assessed using the University of York's CRD checklist for RCTs,[41] while non-RCTs and observational studies were assessed using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool.[42]

Quality assessment was conducted by one reviewer and the conclusions were confirmed by a second reviewer. The ERG considers these methods to be appropriate.

4.1.6 Evidence synthesis

The CS[1] (Section B.2.8, page 60) states that meta-analysis was not performed because the ADAURA RCT[35] was the only relevant clinical trial identified. The ERG agrees that this is appropriate.

The CS[1] (Section B.2.9, page 60) states that an indirect comparison is not necessary because the ADAURA RCT[35] includes the relevant comparator (placebo plus active monitoring). The ERG agrees that this is appropriate.

4.1.7 Studies of adjuvant therapies for EGFRm-positive NSCLC from broader review

CS Appendix D[36] (Section D.2, page 24) states that the broader review of adjuvant therapies for EGFRm-positive NSCLC identified 26 publications relating to 13 studies. Only one of these, the ADAURA RCT,[35] relates to osimertinib and is included in the main CS.[1] The CS (Section B.2.2 Table 5, page 34) notes that the key publication for ADAURA (Wu *et al*., 2020)[35] was not identified in the systematic review as it was published more recently than the search date.

The 13 studies of adjuvant therapies from the broader review are summarised in Table 4 for background information, though these are not used further in the CS.[1] Of these, in addition to the ADAURA RCT of osimertinib,[35] the following RCTs assessed other EGFR TKIs: three RCTs of adjuvant gefitinib (ADJUVANT/CTONG1104;[28] Li 2014;[43] NCT00049543[44]); two RCTs of adjuvant erlotinib (EVAN;[27] RADIANT[24]) and one RCT of adjuvant icotinib (NCT02430974[45]).

Table 4: Studies of adjuvant therapies for EGFRm-positive NSCLC from broader review (adapted from CS Appendix D, Table 9)

Study name	Design	Intervention	Comparator	References
Adjuvant TKI trials				
ADAURA[a]	RCT	Adjuvant osimertinib	Placebo	• AstraZeneca Clinical Study Report for ADAURA (2020)[37] • WHO International Clinical Trials Registry entry (2015)[46] • Herbst 2020 (conference abstract)[47] • ClinicalTrials.gov entry (2015)[48] • Tsuboi 2019 (conference abstract)[49] • Wu 2018 (study protocol)[50]
ADJUVANT / CTONG1104	RCT	Adjuvant gefitinib	Chemotherapy	• ClinicalTrials.gov entry (2011)[51] • Wu 2020[28] • Xu 2019[23] • Zhong 2017[26]
EVAN	RCT	Adjuvant erlotinib	Chemotherapy	• Yue 2018[27]
Li 2014	RCT	Adjuvant gefitinib + chemotherapy	Chemotherapy	• Li 2014[43]
Goss 2013 (NCT00049543 / NCIC CTG BR19)	RCT	Adjuvant gefitinib	Placebo	• Goss 2013[44] • ClinicalTrials.gov entry (2002)[52]
RADIANT	RCT	Adjuvant erlotinib	Placebo	• WHO International Clinical Trials Registry entry (2006)[53] • Kelly 2015[24]
SELECT	Single-arm study	Adjuvant erlotinib	-	• Pennell 2019[25]
Yao 2016	Retrospective study	Adjuvant icotinib	-	• Yao 2016[54]
Feng 2015 (NCT02430974)	RCT	Adjuvant icotinib + chemotherapy	Chemotherapy	• Feng 2015[45] • ClinicalTrials.gov entry (2015)[55]
Other adjuvant trials				
JBR.10	RCT	Adjuvant chemotherapy	Observation	• Tsao 2011[56]
JIPANG	RCT	Comparison of two adjuvant chemotherapies	Comparison of two adjuvant chemotherapies	• Kenmotsu 2020[57] • Kenmotsu 2019[58] • Tsuboi 2019[58]
Kim 2017	Single-arm study	Adjuvant chemotherapy	-	• Kim 2017[59]
Zhu 2019	Retrospective study	Adjuvant radiotherapy	-	• Zhu 2019[60]

RCT - randomised controlled trial; WHO - World Health Organization
a The key publication for ADAURA (Wu et al., 2020)[35] was not identified in the company's systematic review as it was published more recently than the search date

4.1.8 Ongoing studies

The CS[1] (Section B.2.11, page 62) states that the ADAURA trial[35] is currently ongoing, with the final analysis anticipated in [redacted]. The CS states that no other ongoing studies of osimertinib are relevant to this indication.

An editorial identified by the ERG[61] highlights two ongoing trials of osimertinib plus chemotherapy, although neither of these is in the adjuvant setting:

- NeoADAURA (NCT04351555): neoadjuvant therapy before resection in patients with EGFRm-positive, stage II-IIIB NSCLC with 3 arms: osimertinib plus chemotherapy vs. osimertinib monotherapy vs. chemotherapy alone
- FLAURA2 (NCT04035486): first-line therapy for EGFRm-positive, metastatic NSCLC: osimertinib plus chemotherapy vs. osimertinib monotherapy.

4.2 Critique of the key clinical study

The CS[1] (Section B.2.1, page 33) states that the systematic review identified a single RCT of osimertinib in the population of interest to the submission: the ADAURA trial.[35] The CS[1] also states that additional supporting evidence in the submission comes from the FLAURA RCT of osimertinib versus erlotinib or gefitinib in first-line locally-advanced and metastatic NSCLC,[38, 39, 62, 63] and the US real-world evidence CancerLinQ database.[64] These two studies were not retrieved from the clinical systematic review and are not discussed in the clinical section of the CS; instead, they are used to support the economic modelling and are presented in the CS Appendix L.[65] These studies are described further in Section 5.2.3.

4.2.1 Study design: ADAURA

The characteristics of the ADAURA trial[35] are summarised in Table 5. Exclusion criteria for the trial are presented in Table 6. The ADAURA trial compared adjuvant osimertinib versus placebo (established clinical management) in adults with non-squamous completely resected EGFRm-positive NSCLC (Ex19del or L858R mutation), with post-surgical stage IB−IIIA and WHO PS 0-1, treated with or without adjuvant chemotherapy. The ERG's clinical advisors stated that the inclusion criteria appear appropriate for an adjuvant study. Treatment duration was planned for 3 years or until disease recurrence or fulfilment of discontinuation criteria.[37] However, the study was unblinded two years early due to overwhelming efficacy with osimertinib; the results in the CS[1] are based on this interim analysis. ADAURA was conducted across [redacted] in 24 countries across Europe, Asia-Pacific, North America, and South America; however, the number of UK sites is not reported in the CS.

The following outcomes were reported in the CS[1] for the ADAURA study:

- OS
- DFS
- Sites, rates and timing of recurrence
- CNS recurrence (*post hoc* endpoint)
- TTD (reported in the cost-effectiveness section of the CS)
- HRQoL
- Adverse events.

Table 5: Study characteristics of ADAURA (adapted from CS, Tables 5, 6 and 7 and Figure 5)

Trial name Key refs	Design	Population	Intervention (N)	Comparator (N)	Treatment duration	Stratification factors	Countries	Analysis populations	Subgroup analyses (DFS)
ADAURA Wu *et al.*, 2020[35] Tsuboi *et al.*, 2020[66] CSR, interim analysis[37]	RCT (Phase III, double-blind, multicentre, ongoing)	Adults aged ≥18 (or aged ≥20 in Japan and Taiwan) WHO PS 0–1 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	Osimertinib 80mg once daily (N=339) Reduced to 40mg/day if clinically significant AEs or unacceptable toxicity	Placebo (established clinical management) (N=343)	Duration: 3 years or until disease recurrence or fulfilment of discontinuation criteria Unblinded two years early due to overwhelming efficacy with osimertinib	Stage (IB vs. II vs. IIIA) EGFRm type (Ex19del vs. L858R Race (Asian vs. non-Asian)	[redacted] in 24 countries across Europe, Asia-Pacific, North America, and South America	Overall population (focus of CS): all patients Primary study population): stage II-IIIA	Stage EGFRm type Mutation status Race Adjuvant chemotherapy Gender Age Smoking history

EGFR - epidermal growth factor receptor; Ex19del - exon 19 deletion; NSCLC - non-small cell lung cancer; PS - performance status; WHO - World Health Organization

Table 6: Exclusion criteria for ADAURA (adapted from CS, Table 8)

Exclusion criteria
• Any disallowed treatment (pre-/post-operative/planned radiation therapy for current lung cancer; neo-adjuvant chemotherapy; prior anticancer therapy for NSCLC other than platinum-based doublet post-operative 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 (except 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 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

Planned analyses in ADAURA

The study populations included in statistical analyses of ADAURA[37] are described in Section B.2.4 of the CS[1] (page 45); these are summarised in Table 7. These consisted of the overall population (all randomised patients, stage IB-IIIA, N=682); the safety analysis set (all patients receiving at least one dose of study treatment, N=680) and the primary study population (stage II-IIIA, N=470). The ERG notes that the company's economic analysis is based on the overall population (see Section 5.2). The effectiveness results for ADAURA are presented with 99.12% or 99.06% confidence intervals in order to control for Type 1 errors when there is multiple testing.

Table 7: Analysis groups in ADAURA (adapted from CS, Figure 6 and Section B.2.4)

Analysis population	Description	Osimertinib N	Placebo N	Total N
Overall population (full analysis set)	All randomised patients (stage IB-IIIA) Intention-to-treat basis Main focus of CS	339	343	682
Safety analysis set	All patients receiving at least 1 dose of study treatment	337	343	680
Primary study population	All randomised patients with stage II-IIIA disease	233	237	470

N - number; CS - company's submission

Patient flow and treatment duration in ADAURA

Patient flow in ADAURA[35] at the time of the interim analysis is described in the CS (Section B.2.3.2 pages 41-42 and Figure 6); this is summarised in Table 8. Median duration of treatment exposure was 22.5 months in the osimertinib arm and 18.7 months in the placebo arm, and [redacted]. Of the 682 randomised patients, two patients did not receive their allocated treatment, 73 had completed treatment, 341 were still undergoing treatment and 266 had discontinued treatment.

Table 8: Patient flow in ADAURA (adapted from CS, Figure 6 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 treatment	40	33	73
Ongoing treatment at data cut-off	205	136	341
Discontinued treatment:	92	174	266
Adverse event	36	10	
Patient decision	30	9	
Disease recurrence	24	148	
Other	2	4	
Protocol non-compliance	0	3	
Median duration of treatment exposure	22.5 months	18.7 months	NR

N - number; NR - not reported

Quality assessment of ADAURA

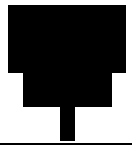
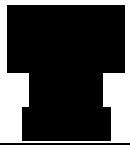
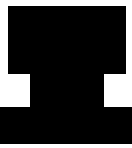
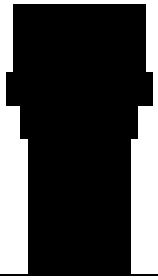
The quality assessment presented in the CS[1] (Section B.2.5, Table 11, pages 47-48) indicates that ADAURA[35] is a high-quality RCT with appropriate randomisation, concealment of treatment allocation, baseline characteristics well-balanced between arms, blinding of care providers, participants and outcome assessors, no unexpected imbalances in drop-outs between arms, reporting of all relevant outcomes, and use of intention-to-treat analysis. The ERG agrees with this assessment and considers ADAURA to be at low risk of bias.

4.2.2 Baseline characteristics: ADAURA

The patient baseline characteristics in ADAURA[35] are reported in the CS[1] (Section B.2.3.3, Table 9 and Table 10, pages 43-44); these are reproduced in Table 9.

In terms of generalisability to a UK population, the ERG's clinical advisors stated that the median age of patients in the study was relatively young for a NSCLC population but may be generalisable to an EGFRm-positive NSCLC population. The clinical advisors also noted [redacted] that there are more females [redacted] than would be expected in a UK population. The company's clarification response[16] (question A5) states that the company's clinical experts considered the ADAURA population to be representative of patients with stage IB–IIIA EGFRm-positive NSCLC in the UK.

Table 9: Key patient demographics and baseline characteristics in ADAURA (reproduced from CS, Table 9 and Table 10)

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 Asian Other Missing		
Smoking status, n (%) Never Former Current		
Median body mass index, kg/m^2 (range)		
WHO performance status, n (%) 0 1		
AJCC stage at diagnosis, n (%) IB IIA IIB IIIA		
EGFR mutations, n (%) Exon 19 deletions L858R		
Histology type, n (%) Adenocarcinoma Acinar Papillary, malignant Malignant Bronchiolo-alveolar Solid with mucous formation Bronchial gland carcinoma (NOS) Carcinoma, adenosquamous, malignant Other		
Lung cancer resection type, n (%) Lobectomy Sleeve resection Bilobectomy Pneumonectomy		
Regional lymph nodes, % N0 N1 N2		
Adjuvant chemotherapy, n (%) Stage IB, received chemotherapy Stage II, received chemotherapy Stage IIIA, received chemotherapy		

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;[35] ADAURA CSR[37]

4.2.3 Effectiveness results: ADAURA

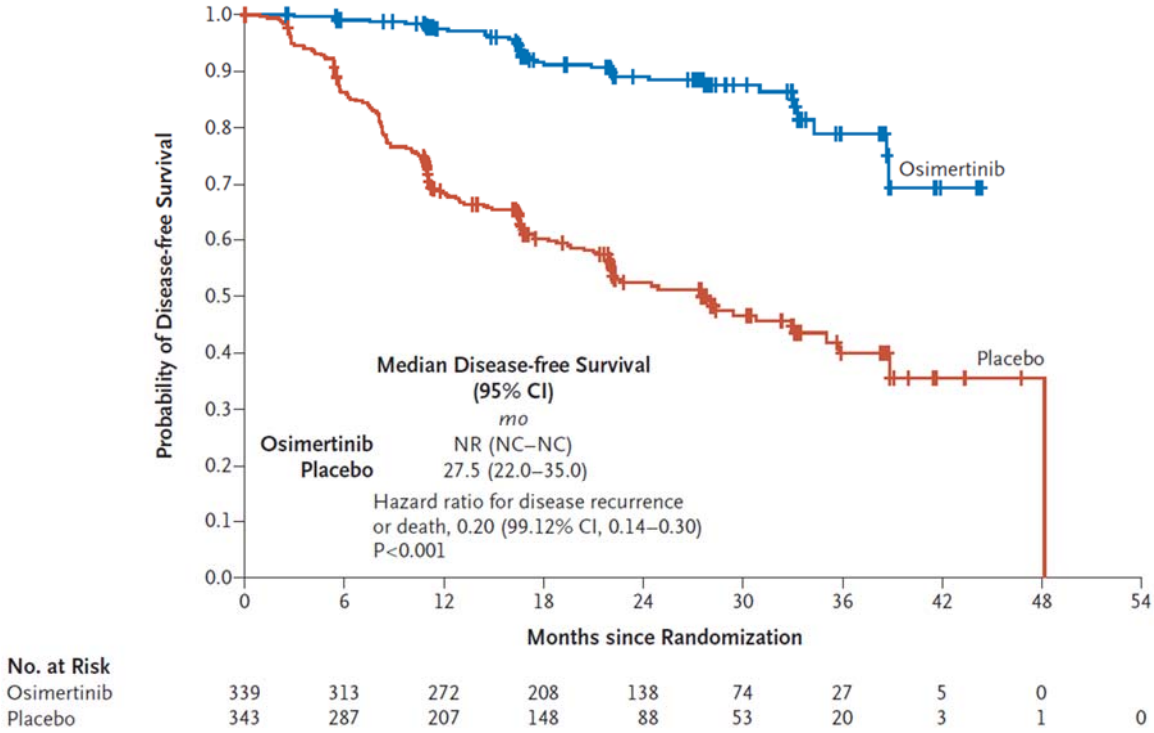
Clinical effectiveness results for ADAURA are presented in Section B.2.6 of the CS[1] (pages 49-59). The results presented are from the interim analysis with a data cut-off of the 17th January 2020, when the trial was unblinded 2 years early. The CS states that an additional efficacy analysis will be conducted approximately 2 years after the interim data cut-off ([redacted]). The CS states that the main population of relevance to the submission is the "overall population", i.e. all randomised patients (stage 1B-IIIA). Data for the "primary study population" (stage II-IIIA) are also presented in the CS. The ERG confirms that the effectiveness data in the CS appear consistent with those in the primary study publications (Wu *et al.*, 2020[35] and Tsuboi *et al.*, 2020[66] for data on CNS metastases).

Disease-free survival: ADAURA

Overall population: DFS outcomes for the overall population are shown in Figure 3. Within the overall population, treatment with osimertinib resulted in significantly longer DFS (hazard ratio [HR]: 0.20; 99.12% confidence interval [CI]: 0.14, 0.30; $p<0.001$). Median DFS was not reached with osimertinib and was 27.5 months in the placebo group. Data presented in Table 12 of the CS[1] indicate that the proportion of patients who were alive and disease-free at 24 months was 89.1% (95% CI: 84.5, 92.4) in the osimertinib group versus 52.4% (95% CI: 46.4, 58.1) in the placebo group, and that [redacted].

Stage II-IIIA population: DFS outcomes for the stage II-IIIA population are shown in Figure 8 of the CS,[1] but are not reproduced here. Within this population, treatment with osimertinib significantly improved DFS in the stage II–IIIA population (HR: 0.17; 99.06% CI: 0.11, 0.26; $p<0.001$). Median DFS was not reached with osimertinib and was 19.6 months in the placebo group.

Figure 3: Kaplan-Meier plot of DFS in ADAURA – overall population (reproduced from CS, Figure 7)

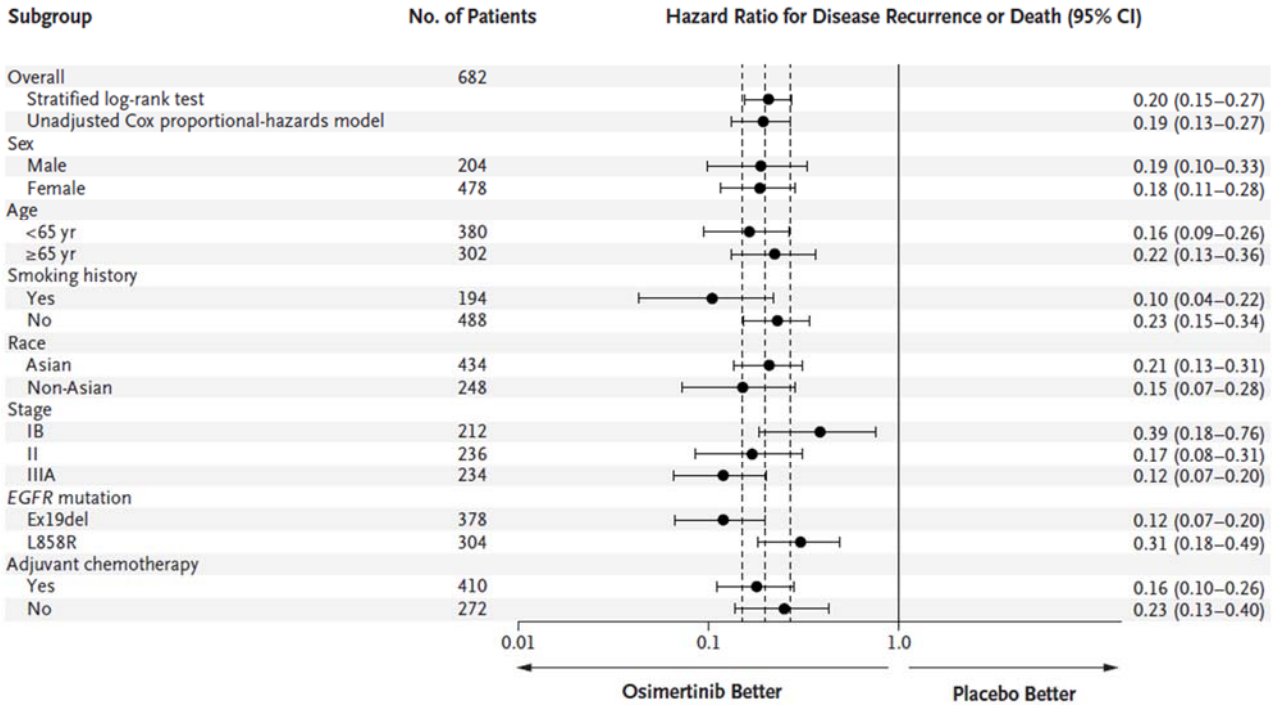


CI - confidence interval; DFS - disease-free survival; NC - not calculable; NR - not reached
Source: Wu et al., 2020[35]

Subgroup analyses for DFS: ADAURA

The CS[1] (pages 50-51) states that the DFS benefit of osimertinib was observed across all pre-defined subgroups, including male/female sex, disease stages IB, II, and IIIA, and patients who had or had not received adjuvant chemotherapy (Figure 4). [redacted]

Figure 4: Subgroup analysis of DFS – overall population (reproduced from CS, Figure 9)



CI - confidence interval; DFS - disease-free survival; EGFR - epidermal growth factor receptor
Source: Wu et al, 2020.[35]

Subgroup analyses for DFS by disease stage: ADAURA

DFS outcomes by disease stage are shown in Table 10. In addition, Kaplan-Meier plots of DFS by disease stage are reported in the ADAURA publication (Wu *et al.*, 2020;[35] supplementary Figure S3).

Table 10: DFS by stage (adapted from CS, page 53, Table 12 and Wu et al, 2020)

Population	Alive and disease-free at 24 months		HR (95% CI)
	Osimertinib	Placebo	
Overall population (stage IB-IIIA)	89%	52%	0.20 (0.14, 0.30)[a]
Stage IB	88%	71%	0.39 (0.18 to 0.76)
Stage II	91%	56%	0.17 (0.08 to 0.31)
Stage IIIA	88%	32%	0.12 (0.07 to 0.20)

CI - confidence interval; HR - hazard ratio
[a]99.12% CI.

Overall survival: ADAURA

Overall population: As stated in the CS[1] (page 54), at the time of the data cut-off, OS data from ADAURA were not mature ( ) with most patients still under survival follow-up . In total, 9 patients (2.7%) in the osimertinib arm and 20 patients (5.8%) in the placebo arm had died by the data cut-off for the interim analysis. OS outcomes for the overall population are shown in Figure 5.

[redacted]

Stage II-IIIA population: OS outcomes for the stage II-IIIA population are shown in Figure 11 of the CS,[1] but are not reproduced here. In the stage II–IIIA population (5.3% data maturity), 3.4% of patients with osimertinib and 7.2% with placebo had died by the data cut-off for the interim analysis (HR: 0.40; 99.98% CI: 0.09, 1.83; [redacted]). Median OS was not calculable in either trial arm.

Figure 5: Kaplan-Meier plot of OS in ADAURA – overall population (reproduced from CS, Figure 10)

[redacted]

OS - overall survival
Source: ADAURA CSR[37]

Type and timing of disease recurrence: ADAURA

Loco-regional and distant recurrences are shown in Table 11. Disease recurrences occurred in fewer patients in the osimertinib arm (11%) than in the placebo arm (46%). Loco-regional recurrences occurred in 7% of patients in the osimertinib arm and 18% of patients in the placebo arm, while distant recurrences occurred in 3% of patients in the osimertinib arm and 23% of patients in the placebo arm (in addition, both local and distant recurrences occurred in 1% of patients in the osimertinib arm and 5% of patients in the placebo arm). [redacted]

Table 11: Type of disease recurrence - overall population (adapted from CS, Table 13)

Recurrences: n (%)	Osimertinib	Placebo
N	339	343
Disease recurrence (total)	37 (11%)	157 (46%)
Local/regional only	23 (7%)	61 (18%)
Distant only	10 (3%)	78 (23%)
Local/regional and distant	4 (1%)	18 (5%)

CI - confidence interval; N - number
Sources: ADAURA CSR,[37] Wu et al., 2020.[35]

CNS recurrence (post-hoc analysis): ADAURA

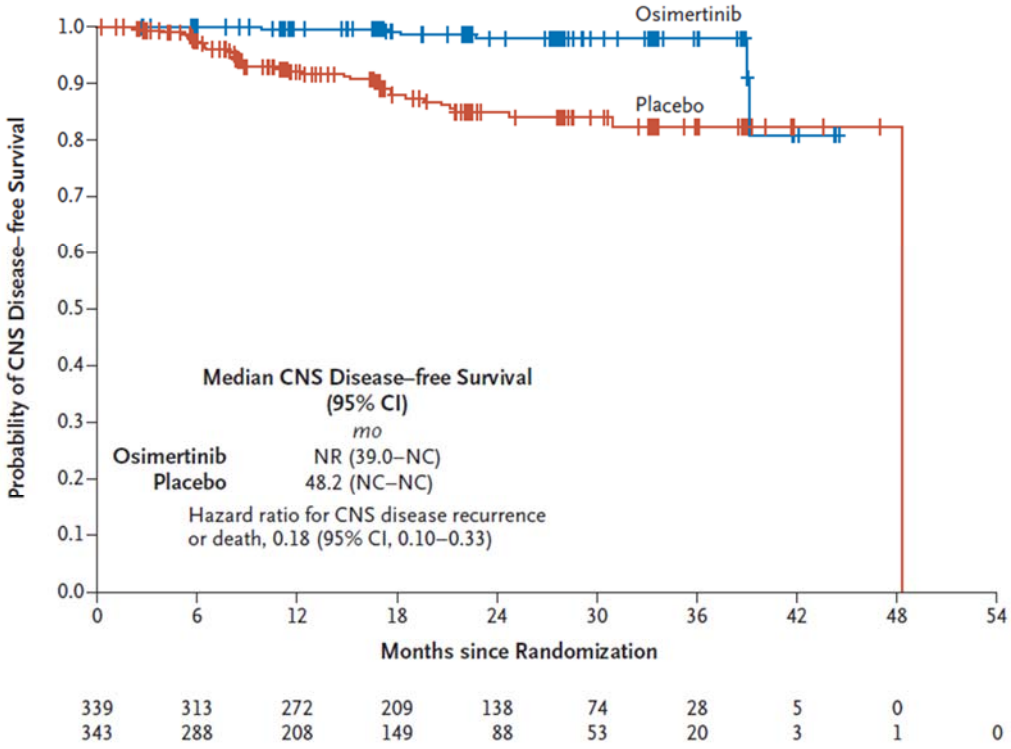
Data relating to CNS recurrence or death are summarised in Table 12. In the overall population, the proportion of patients experiencing CNS events was numerically lower with osimertinib (4 patients; 1.2%) vs. placebo (33 patients; 9.6%). [redacted] A significantly lower risk of CNS recurrence or death was observed with osimertinib compared with placebo: the HR for CNS DFS was 0.18 (95% CI: 0.10, 0.33; $p<0.0001$) in the overall population (Figure 6), [redacted].

Table 12: Summary of CNS recurrence or death – overall population (adapted from CS, Table 14)

n (%)	Osimertinib	Placebo
N	339	343
Any event	6 (1.8%)	39 (11.4%)
CNS recurrence	4 (1.2%)	33 (9.6%)
Death	2 (0.6%)	6 (1.7%)
Hazard ratio (95% CI)	0.18 (0.10, 0.33)	
2-sided *p*-value	<0.0001	

CI - confidence interval; N - number
Sources: ADAURA CSR;[37] Tsuboi et al., 2020[66]

Figure 6: Kaplan-Meier plot of CNS DFS in ADAURA - overall population (reproduced from CS, Figure 12)



CI - confidence interval; CNS - central nervous system; DFS - disease-free survival; NC - not calculable; NR - not reached.
Source: Wu et al., 2020[35]

Health-related quality of life: ADAURA

According to the CS[1] (Section B.2.6.1.3), HRQoL was measured via the 36-Item Short Form Survey (SF-36). The company's clarification response[16] (question A7) highlights that HRQoL data were collected until disease recurrence, treatment completion (3 years) or treatment discontinuation; in other words, HRQoL data were not collected following disease relapse. [redacted]

[redacted]

4.2.4 Safety: ADAURA

The osimertinib safety information presented in the CS[1] (Section B.2.10) focusses on the ADAURA study.[35] In ADAURA, the median duration of treatment exposure in the overall population was 22.5 months in the osimertinib group and 18.7 months in the placebo group. The proportions of patients who received adjuvant platinum-based chemotherapy were similar in the two treatment groups, with approximately 25% of stage IB, 70% of stage II, and 80% of stage IIIA patients receiving adjuvant chemotherapy.

Overview of AEs in ADAURA

In total, 98% of patients in the osimertinib group and 89% in the placebo group reported ≥1 AE during the trial, of which [redacted] and [redacted], respectively, were considered related to treatment (Table 13). Of these, serious adverse events (SAEs) were reported by 16% and 12% of patients treated with osimertinib and placebo, respectively, [redacted] Only one death occurred due to an AE (pulmonary embolism); this occurred in the placebo group.

Dose modifications and treatment discontinuations due to AEs were as follows for the osimertinib and placebo arms, respectively: treatment discontinuations in 11% vs. 3% of patients; dose interruptions in 24% vs. 11% of patients; and dose reductions in 9% vs. 1% of patients.

Table 13: Summary of AEs in ADAURA (adapted from CS, Table 15)

AEs, n (%)	**Osimertinib (N=337)**	**Placebo (N=343)**
Any AE	329 (98)	306 (89)
AEs considered causally-related to treatment†	[redacted]	[redacted]
AEs of CTCAE Grade 3 or higher	[redacted]	[redacted]
AEs of CTCAE Grade 3 or higher considered causally-related to treatment		
Any AE with outcome of death	0	1 (<1)
AEs with outcome of death considered causally-related to treatment†	[redacted]	[redacted]
Any SAE	54 (16)	42 (12)
SAEs considered causally reported to treatment†	[redacted]	[redacted]
Change in treatment/trial continuation due to AEs		
Trial regimen discontinuation	37 (11)	10 (3)
Dose interruption	80 (24)	37 (11)
Dose reduction	29 (9)	3 (1)

AE - adverse event; CTCAE - Common Terminology Criteria for Adverse Events; SAE - serious adverse event; N - number
† As evaluated by the trial investigator
Source: Wu et al., 2020;[35] ADAURA CSR[37]

Most common AEs in ADAURA

The most common AEs (reported by ≥10% of patients in either treatment group) are shown in Table 14. AEs reported by ≥10% more patients with osimertinib than placebo included: diarrhoea; paronychia (infection of skin around nails); dry skin; pruritis (itch) and stomatitis (sore mouth).

Table 14: Most common AEs (≥10% of patients in either treatment group) in ADAURA (reproduced from CS, Table 16)

AEs, n (%)	Osimertinib (N=337)		Placebo (N=343)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	156 (46)	8 (2)	68 (20)	1 (<1)
Paronychia	85 (25)	3 (1)	5 (1)	0
Dry skin	79 (23)	1 (<1)	22 (6)	0
Pruritis	65 (19)	0	30 (9)	0
Cough	62 (18)	0	57 (17)	0
Stomatitis	59 (18)	6 (2)	14 (4)	0
Nasopharyngitis	47 (14)	0	35 (10)	0
Upper respiratory tract infection	45 (13)	2(1)	35 (10)	0
Decreased appetite	44 (13)	2 (1)	13 (4)	0
Mouth ulceration	39 (12)	0	8 (2)	0
Dermatitis acneiform	37 (11)	0	16 (5)	0

AE - adverse event; N - number
Source: Wu et al., 2020;[35] ADAURA CSR[37]

Grade ≥3 AEs in ADAURA

AEs of Grade ≥3 reported by 2 or more patients in either treatment arm are listed in Table 15 (clarification response,[16] question A9).

Table 15: Common CTCAE Grade ≥3 AEs in ADAURA reported by ≥2 patients in either arm (reproduced from company's clarification response, Table 5)

Patients, n (%)	Osimertinib (N=337)	Placebo (N=343)
[redacted]		

AE - adverse event; CTCAE - Common Terminology Criteria for Adverse Events

Grade 4 AEs in ADAURA

All Grade 4 AEs are listed in Table 16 (company's clarification response,[16] question A9).

Table 16: All CTCAE Grade 4 AEs in ADAURA (reproduced from company's clarification response, Table 6)

Patients, n	Osimertinib (N=337)	Placebo (N=343)
[redacted]		

AE - adverse event; CTCAE - Common Terminology Criteria for Adverse Events

AEs of special interest in ADAURA

AEs of special interest for osimertinib include ILD (pneumonitis) and cardiac AEs (Table 17). The data presented here are from the CS[1] (Section B.2.10, page 61) and from Wu *et al.* (2020).[35] ILD events were reported in 10 (3%) patients treated with osimertinib and 0 patients in the placebo group; all events were mild or moderate in severity, with one event reported as serious. The company's clarification response[16] (question A8) states that the patient with a serious ILD event was hospitalised in case of symptomatic worsening; however, this patient and all patients with ILD events were reported to have recovered. Cardiac AEs were reported in 16 (5%) patients treated with osimertinib and 10 (3%) patients treated with placebo; these were Grade ≥3 in 3 (0.9%) with osimertinib and 1 (0.3%) with placebo, and one serious event (pulmonary edema) occurred in the osimertinib group.

Table 17: AEs of special interest in ADAURA

AEs, n (%)	Osimertinib (N=337)		Placebo (N=343)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Interstitial lung disease / pneumonitis	10 (3) (1 serious)	0	0	0
Cardiac AEs (ejection fraction decrease, cardiac failure, pulmonary edema, cardiomyopathy)	16 (5%) (1 serious; pulmonary edema)	3 (0.9%)	10 (3%)	1 (0.3%)

AE - adverse event; N - number
Source: CS[1] and Wu et al., 2020 (supplement).[35]

4.3 Critique of trials identified and included in the indirect comparison

The CS[1] (Section B.2.9, page 60) states that an indirect comparison was not performed because the ADAURA RCT[35] includes the relevant comparator (placebo plus active monitoring). The ERG agrees that this is appropriate.

4.4 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake any additional work relating to estimating the clinical effectiveness of osimertinib.

4.5 Discussion and conclusions for clinical effectiveness

4.5.1 Summary of effectiveness evidence

The clinical effectiveness evidence for adjuvant osimertinib is based on the ADAURA RCT of adjuvant osimertinib versus placebo (with or without adjuvant chemotherapy in both arms) for people with completely resected stage IB−IIIA EGFRm-positive NSCLC.[37] Treatment duration in ADAURA was planned for 3 years or until disease recurrence or fulfilment of discontinuation criteria. However, the trial was unblinded two years early due to overwhelming efficacy with osimertinib for DFS, and the data in the CS[1] are based on this interim analysis. Median duration of treatment was 22.5 months in the osimertinib arm and 18.7 months in the placebo arm.

There was a statistically significant DFS benefit for osimertinib: HR 0.20 (99.12% CI 0.14, 0.30; $p<0.001$). The statistically significant DFS benefit was observed across all pre-defined subgroups, including male/female sex, disease stages IB, II, and IIIA, and patients who had or had not received adjuvant chemotherapy. However, the magnitude of benefit was smaller for stage IB disease. There were fewer distant recurrences and CNS recurrences in the osimertinib arm than in the placebo arm. In addition, distant and CNS recurrences accounted for a smaller proportion of the total recurrences in the osimertinib arm than in the placebo arm. Recurrences in the osimertinib arm included: total recurrence 11%; loco-regional recurrence 7%; distant recurrence 3%; both loco-regional and distant 1%; CNS recurrence 1%. Recurrences in the placebo arm included: total recurrence 46%; loco-regional recurrence 18%; distant recurrence 23%; both loco-regional and distant 5%; CNS recurrence 11%.

The main limitation of the ADAURA trial[37] is that the OS data are immature, with only 9 deaths (2.7%) in the osimertinib arm and 20 deaths (5.8%) in the placebo arm; [redacted]. Therefore, it is uncertain whether the statistically significant DFS benefit will translate into a significant OS benefit.

4.5.2 Limitations of effectiveness evidence

Limitations of the clinical evidence are discussed here, with reference to commentaries on the ADAURA trial (Gyawali *et al.*, 2021;[67] Remon *et al.*, 2021;[68] and Uprety *et al.*, 2021[69]). Gyawali *et al.*[67] suggest that the goal of an adjuvant therapy should be to improve long-term survival. Gyawali *et al.*[67] and Uprety *et al.*[69] also note that other adjuvant TKIs in EGFRm-positive NSCLC have demonstrated DFS benefits which have not translated to an OS benefit, and that a similar pattern has been observed for some adjuvant treatments in other cancers. In addition, they note that it is uncertain

whether the magnitude of DFS benefit will remain as large once longer follow-up has occurred. Conversely, Remon *et al*.[68] note that the delay in disease recurrence, especially CNS recurrence, observed in ADAURA may be considered a positive outcome in itself.

Gyawali *et al*.[67] also suggest that a question which should be asked is whether adjuvant osimertinib for all patients leads to superior OS versus treatment with osimertinib upon recurrence. The authors note that, for a fair comparison of these approaches, patients in the control arm of ADAURA[37] should have received osimertinib upon recurrence; it is unclear what proportion of patients did so. Nonetheless, the ERG notes that the available OS data from the interim data-cut are very limited.

Gyawali *et al*.[67] and Uprety *et al*.[69] further note that ADAURA[37] did not require staging of patients using positron emission tomography / computed tomography (PET/CT) or brain magnetic resonance imaging (MRI), which may have effectively understaged some patients, meaning that some of the effect of adjuvant osimertinib may have been in suppressing small-volume metastatic disease. A similar criticism is made regarding the prevention of CNS metastases; the ADAURA publication[35] does not report the proportion of patients who received a brain MRI, which is more sensitive than head CT for detecting CNS metastases; therefore, an improvement in CNS relapses could mean that in some patients, osimertinib is treating undetected small brain metastases.

All three commentaries[67-69] also note that, despite the reasonable tolerability of adjuvant osimertinib, low-grade AEs such as diarrhoea, paronychia and stomatitis can still be quite debilitating when the therapy is given over several years, especially considering that some patients would have been cured without adjuvant therapy. The ERG's clinical advisors also noted that there is little available evidence around the possible late effects of adjuvant osimertinib treatment, which is relevant if some patients are expected to experience long-term survival.

4.5.3 Summary of safety evidence

The safety evidence for adjuvant osimertinib is based on the ADAURA RCT.[37] SAEs were reported by 16% and 12% of patients in the osimertinib and placebo arms, respectively, of which [redacted] and [redacted] respectively were considered related to treatment. Grade ≥3 AEs were reported by [redacted] and [redacted] of patients in the osimertinib and placebo arms, respectively, of which [redacted] and [redacted], respectively, were considered related to treatment. Only one death occurred due to an AE (pulmonary embolism); this occurred in the placebo group. Dose modifications and treatment discontinuations due to AEs were as follows for the osimertinib and placebo arms, respectively: treatment discontinuations in 11% vs. 3%; dose interruptions in 24% vs. 11%; and dose reductions in 9% vs. 1%.

AEs reported by ≥10% more patients with osimertinib than placebo included: diarrhoea; paronychia (infection of skin around nails); dry skin; pruritis (itch) and stomatitis (sore mouth). Decreased appetite, mouth ulceration and dermatitis acneiform were also numerically more common in the osimertinib arm than the placebo arm.

AEs of special interest for osimertinib include ILD (pneumonitis) and cardiac AEs. ILD events were reported in 10 (3%) patients treated with osimertinib and 0 patients in the placebo group; all events were mild or moderate in severity, with one event reported as serious (involving hospitalisation). However, all patients with ILD events were reported to have recovered. Cardiac AEs were reported in 16 (5%) patients treated with osimertinib and 10 (3%) patients treated with placebo; these were Grade ≥3 in 3 (0.9%) patients with osimertinib and 1 (0.3%) patient with placebo, and one serious event (pulmonary edema) occurred in the osimertinib group.

5 COST EFFECTIVENESS

This chapter provides a summary and critique of the company's economic analyses of osimertinib for the adjuvant treatment of EGFRm-positive non-small-cell lung cancer after complete tumour resection, together with additional exploratory analyses undertaken by the ERG. Section 5.1 summarises the company's SLR of existing economic analyses of adjuvant treatments for stage IB–IIIA NSCLC. Section 5.2 presents a detailed description of the methods and results of the company's original submitted economic model. Section 5.3 presents the ERG's critical appraisal of the company's original model and summarises the results of an updated version of the model provided following the clarification round. Section 5.4 presents the methods and results of the exploratory analyses undertaken by the ERG using the updated model. Section 5.5 presents a discussion of the available economic evidence for adjuvant osimertinib.

5.1 Company's review of cost-effectiveness evidence

5.1.1 Summary and critique of the company's search strategy

The company performed systematic literature searches for (i) published cost-effectiveness studies of patients who have stage IB-IIIA NSCLC; (ii) HRQoL studies and (iii) cost and resource use studies (CS Appendices G, H and I,[36] respectively). All three sets of searches were undertaken in November 2020.

The cost-effectiveness studies search strategy (CS Appendix G[65]) involved one search across the following sources: MEDLINE [via Ovid]; MEDLINE In-Process [via Ovid]; Embase [via Ovid]; the Cochrane Database of Systematic Reviews [via Wiley]; the Cochrane Central Register of Controlled Trials [via Wiley]; the Health Technology Assessment database [via Wiley]; the Database of Abstracts of Reviews of Effects [via Wiley]; the NHS Economic Evaluation Database [Via Wiley] and EconLit [via Ovid]. The search was limited to studies published after 2010. The company searched several key conference abstract websites in the last three years (2017 to 2020) via Embase.com, including: ESMO; ELCC; ASCO; AACR; ECCO, and WCLC. The company also hand-searched grey literature and web site sources, including: the Cost-Effectiveness Analysis (CEA) Registry, Research Papers in Economics (RePEc) for working papers; the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) presentations database online; the HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA), the EuroQol website and UK HTA agency websites (NICE, Scottish Medicines Consortium [SMC], All Wales Medicines Strategy Group [AWMSG]).

The company's search strategy comprises disease terms combined with economics and modelling search filters which were translated consistently across the databases. The origin of the search filters used is not stated in the CS; however, there were no apparent important errors and the ERG considers that the search is comprehensive.

The HRQoL studies search (CS Appendix H[65]) involved the same sources as those consulted in the cost-effectiveness searches. The strategy comprised disease terms combined with a HRQoL and utilities search filter in MEDLINE, Embase and the Cochrane Library. The searches were limited to studies published after 2010. The source of the search filters is unclear, but the ERG considers the search terms used to be comprehensive, transparent and reproducible.

The cost and resource use studies search (CS Appendix I[65]) also involved the same sources as those consulted in the cost-effectiveness searches. The strategy comprises disease terms combined with a cost and resources search filter in MEDLINE, Embase and Cochrane Library. The searches were limited to studies published after 2010. The ERG considers the search terms used to be comprehensive, transparent and reproducible.

5.1.2 Summary of company's review findings

The results of the company's SLR of published economic analyses are summarised in CS Appendix M.[36] The company's searches identified 627 citations. Following the removal of 90 duplicates, the abstracts and titles of 569 studies were sifted and the full texts of 42 studies were reviewed. However, all of these studies were excluded from the review as none related to the economic analysis of adjuvant treatments in completely resected, stage IB–IIIA EGFRm-positive NSCLC (with or without adjuvant chemotherapy). The ERG agrees that the excluded full texts are not directly relevant to the decision problem for this appraisal, but notes that this is unsurprising given the specific characteristics of the population defined in the inclusion criteria. It is possible that some of the model-based studies identified in the review could have been used to inform the model structure and/or parameters.

5.2 Summary of the company's submitted economic evaluation

This section describes the methods and results of the company's original submitted model. Following the clarification process, the company submitted an updated model which includes the correction of several errors and which addresses several other concerns raised by the ERG.[16] The company's updated model and its results are summarised separately in Section 5.3.5.

5.2.1 Scope of the company's economic analysis

As part of its submission to NICE,[1] the company submitted a fully executable health economic model of adjuvant osimertinib, programmed in Microsoft Excel®. The scope of the company's model is summarised in Table 18. 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[37] as well as external sources (the CancerLinQ database[64] and the FLAURA trial[63]). The economic analysis was undertaken from the perspective of the National Health Service (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 2018/2019 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 18: Scope of 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	2018/19 (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 trial population of ADAURA.[37] 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 for osimertinib at 3 years, based on the design of the ADAURA trial.[37] [redacted]

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 relapse.

Downstream treatments following loco-regional or distant relapse

Table 19 summarises the treatment pathways following loco-regional or distant recurrence assumed in the company's model. In both treatment groups, the model assumes that patients who experience loco-

regional recurrence will receive four 21-day cycles of pemetrexed plus cisplatin (PDC) plus radiotherapy (500mg pemetrexed IV, 75mg cisplatin IV, plus 20 fractions of radiotherapy given over 28 days).

In the active monitoring comparator group, all patients who develop distant metastases are assumed to receive osimertinib as first-line treatment in the metastatic setting (80mg daily). Within the intervention group, all patients who develop distant metastases within 5 years of starting adjuvant osimertinib treatment 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 5-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). 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); patients who received osimertinib in the first-line metastatic setting are assumed to receive five 21-day cycles of PDC (500mg pemetrexed IV, 75mg cisplatin IV) in the second-line setting. The ERG notes that other treatments may be used for loco-regional recurrence (LRR) and distant metastases which are not included in the company's modelled pathway (see Section 5.3.4).

Table 19: Downstream treatment pathway assumed following adjuvant osimertinib and active monitoring

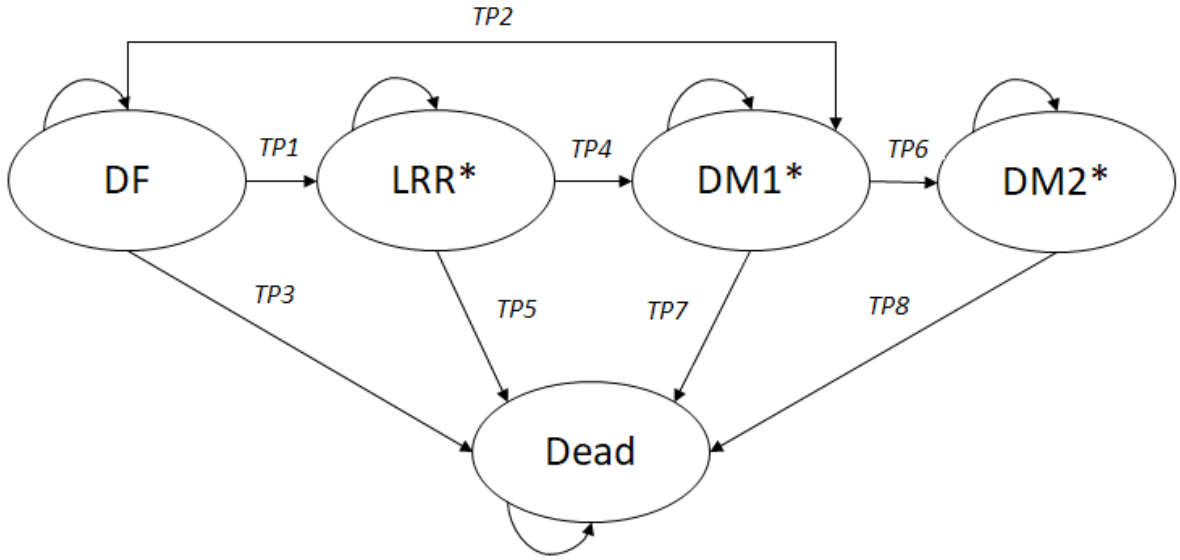
Model treatment group	Re-treatment pathway	Treatment for LRR	First-line treatment for distant metastases	Second-line treatment for distant metastases
Adjuvant osimertinib	No*	4 cycles PDC plus radiotherapy	5 cycles PDC‡	4 cycles of docetaxel§
	Yes†	4 cycles PDC plus radiotherapy	Osimertinib	5 cycles PDC‡
Active monitoring	N/a	4 cycles PDC plus radiotherapy	Osimertinib	5 cycles PDC‡

DF- disease-free; LRR- loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; PDC- pemetrexed plus cisplatin
** All patients progressing before 5 years and 50% of patients after 5 years since starting adjuvant treatment (at model entry)*
† 50% of patients progressing after 5 years since starting adjuvant osimertinib (at model entry)
‡ Five 21-day cycles corresponds to 3.8 model cycles
§ Four 21-day cycles corresponds to 3 model cycles

5.2.2 Model structure and logic

The company's economic analysis adopts a semi-Markov model approach, with some adjustment for competing risks. The model 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 7).

Figure 7: 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*

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 3 years, based on the observed time to treatment discontinuation data from ADAURA[37] (note – this is not structurally linked to any model health state). The following health state transitions are permitted during each 28-day 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 model entry. These sub-models apply matrix multiplication to calculate the probability of remaining in the health state conditional on the time since entry into that state.

Transitions out of the DF state to other alive states (Figure 7, TP1 and TP2) are modelled using parametric survival models fitted to data on DFS from the ADAURA trial.[37] The transition from LRR to DM1 (Figure 7, TP4) is modelled using external data from CancerLinQ.[64] The probability of dying in DF and LRR (Figure 7, TP3 and TP5) is modelled using age- and sex-matched general population life tables;[40] 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 7, 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-positive NSCLC).[63] 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*.[70] 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.[40]

The model includes a key assumption whereby after 5 years, the predicted probabilities of relapse (either loco-regional or distant) applied in the DF health state of both treatment groups are reduced by 95%. This increases the probability that patients remain disease-free and thus continue to have no excess risk of NSCLC-related mortality; these patients also incur no further treatment or monitoring costs after this timepoint. This cure assumption does not apply to patients who have already developed loco-regional or distant recurrence, and disease-free patients are still subject to a small risk of experiencing recurrence beyond this timepoint.

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 metastases states, and a higher value is applied in DM1 compared with DM2. The same utilities are applied in both treatment groups. The model also includes a short-term QALY loss to reflect AEs associated with adjuvant treatment which is 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 recurrence. Health state utilities are adjusted for increasing age.

The model includes costs associated with: (i) drug acquisition and administration (adjuvant treatment and downstream treatments for loco-regional and metastatic recurrences); (ii) monitoring costs; (iii) health state resource use; (iv) managing AEs (applied as a once-only cost); (v) EGFR mutation testing and (vi) end-of-life care.

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-positive 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; these models are described in detail in Section 5.2.3.

- After 5 years since model entry, the predicted probabilities of transitioning from DF to LRR and DM1 are assumed to be reduced by 95%; 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 state receive active first-line therapy for metastatic disease and all patients who enter the DM2 state receive active second-line therapy.
- All patients in the active monitoring group are assumed to receive osimertinib as first line treatment for distant metastases.
- After 5 years since initiating adjuvant treatment with osimertinib, the model assumes that 50% of patients who progress to DM1 will be re-treated with osimertinib.
- Outcomes for patients receiving chemotherapy for metastases are based on outcomes data from the gefitinib/erlotinib arm of the FLAURA trial.[63]
- Outcomes for patients receiving osimertinib in the metastatic setting are assumed to be independent of prior treatment with osimertinib in the adjuvant setting. The model assumes a lifetime treatment effect for osimertinib in the metastatic setting.
- Health utility in the DF and LRR states is assumed to be equivalent and is consistently assumed to be higher than that for the age- and sex-matched general population[71] in every model cycle.
- Additional monitoring costs for osimertinib are assumed to be zero. PDC and docetaxel are assumed to require monitoring via liver function, renal function and blood tests.
- Only Grade 3/4 AEs experienced by at least two patients in ADAURA[37] 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 [redacted] of patients who progress to distant metastases in the adjuvant osimertinib and active monitoring groups, based on the ADAURA trial.[37] This is assumed to lead to additional costs.
- Vial sharing is assumed for intravenous (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 98.9%, based on data from the ADAURA trial.[37]

5.2.4 Evidence used to inform the model parameters

Table 20 summarises the evidence sources used to inform the parameters in the company's base case model; these are discussed in detail in the subsequent sections.

Table 20: Evidence used to inform the company's model

Parameter group	Source
Patient characteristics	Mean age and proportion of patients who are male taken from ADAURA.[37]
Transitions from DF to LRR and DM1 (TP1, TP2)	Adjuvant osimertinib group: ADAURA, osimertinib group[37] Active monitoring group: ADAURA, placebo group[37]
Cure assumption (assumed reduction in risk of relapse and associated timepoint)	Assumed reduction in risk based on company's assumption;[1] timepoint for reduction in risk based on input from clinical experts (see clarification response,[16] question B4)
Transition from LRR to DM1 (TP4)	Both groups: CancerLinQ[64]
Transitions between DM1, DM2 and dead (TP6, TP7, TP8)	Adjuvant osimertinib group, no re-treatment: FLAURA TKI arm[63] Adjuvant osimertinib group, re-treatment: FLAURA osimertinib arm[63]* Active monitoring group: FLAURA osimertinib arm[63] DM1 to dead (TP7) for both groups based on pooled TKI and osimertinib data from FLAURA[63]
Re-treatment probability	Company's assumption, ratified by clinical experts (see clarification response,[16] question B5)
Transitions from DF and LRR to dead (TP3, TP5)	ONS life tables[40]
Health state utility values	DF and LRR: SF-36 data from ADAURA mapped to EQ-5D-3L.[37] DM1: EORTC QLQ-C30 data from FLAURA[63] mapped to EQ-5D-3L.[29] DM2: Labbé *et al*.[72] AE disutilities: Nafees *et al.*[73] and TA653.[34]
Osimertinib acquisition costs	Cost per pack in adjuvant/metastatic settings - CS.[1] Total osimertinib acquisition costs modelled using empirical TTD function from ADAURA[37] (maximum duration = 3 years).
PDC/docetaxel acquisition costs (including premedications)	BNF[74] and eMIT[75]
Radiotherapy cost per fraction (for LRR)	NHS Reference Costs 2018/19[76]
RDI	Osimertinib: ADAURA[37] and FLAURA;[63] RDI for PDC and docetaxel assumed to be 100%.
Drug administration costs	PSSRU[77] and NHS Reference Costs 2018/19[76]
PDC/docetaxel monitoring costs	NHS Reference Costs 2018/19[76]
Health state management costs (DF, LRR, DM1 and DM2)	Andreas *et al.*[14] with additional assumptions. Unit costs taken from NHS Reference Costs 2018/19[76]
CNS metastases management and radiotherapy (for DM1/DM2)	Reference Costs 2018/19;[76] PSSRU;[77] NICE TA536[78] and Royal College of Radiologists report[79]
EGFRm testing costs	NICE DG9,[80] uplifted using HCHS indices[77]
Costs of managing AEs (adjuvant setting only)	Frequency of AEs taken from ADAURA.[37] Unit costs taken from NHS Reference Costs 2018/19[76]
Terminal care costs	Brown *et al.*,[81] NHS Reference Costs 2018/19,[76] PSSRU[77] and Marie Curie report[82]

TP - transition probability; DF - disease-free; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; RDI - relative dose intensity; PDC - pemetrexed plus cisplatin; TTD - time to treatment discontinuation; HCHS - Hospital and Community Health Services; 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; DG - diagnostics guidance

** The company's model includes an error whereby outcomes for patients re-treated with osimertinib are assigned the risk of transitioning from DM1 to DM2 from the TKI control arm of FLAURA (see Section 5.3.4)*

Patient characteristics

Patient characteristics are based on those for the overall population of the ADAURA trial.[37] 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 by increasing age.

Transition probabilities

Summary of transitions and data sources

The company's model includes nineteen transition probabilities, including eight transitions for each treatment group (Figure 7, TP1 to TP8) and a further three transitions for patients who receive adjuvant osimertinib and are subsequently re-treated with osimertinib in the metastatic setting (Figure 7, TP6-TP8 re-treatment).

The transition probabilities for patients who leave the DF state and survive (TP1 and TP2) were estimated using parametric survival models fitted to data from ADAURA.[37] Owing to immaturity of the data from this source, external data were required to estimate all other transition probabilities. The company obtained data from the CancerLinQ database[64] and the FLAURA trial[63] to inform the majority of the other transition probabilities (TP4, TP6, TP7 and TP8). General population life tables[40] were used to inform transitions from DF and LRR to dead (TP3 and TP5, respectively).

CancerLinQ[64] is a real-world database which collects electronic health record data from US cancer patients. A retrospective analysis of data from CancerLinQ from 1 January 2014 to 31 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-positive NSCLC in stage IB–IIIA following tumour resection and who had experienced loco-regional recurrence [redacted]

FLAURA (NCT02296125)[63] 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-positive NSCLC (stage IIIB or IV) that is not amenable to curative surgery or radiotherapy. This study formed the basis of previous NICE TA654 (osimertinib for untreated EGFRm-positive NSCLC).[29]

The CS[1] (Section B.3.3.1) states that a panel of six UK clinicians consulted by the company were satisfied that the data from ADAURA[37] are generalisable to UK practice and that the data from CancerLinQ[64] and FLAURA[63] are appropriate and generalisable to the target population.

A total of ten parametric survival models were fitted to the available time-to-event data, as summarised in Table 21. When survival data from two arms of a trial were modelled, the same parametric form was applied in both groups, based on recommendations given in NICE Decision Support Unit (DSU) Technical Support Document (TSD) Number 14.[83] Whilst the company assessed the proportional hazards assumption for each transition, models were fitted separately to data for each arm, thereby avoiding assumptions of proportional hazards. 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.

Table 21: Summary of parametric survival models used to populate the transition probabilities in the company's model

Dataset	Trial arm	N patients	Event	N events	Competing events censored	Parametric model	Transition(s) used in model treatment group
ADAURA (overall population)[37]	Osimertinib	339	LRR	23	DM1, death	Log-normal	TP1 Osi : DF to LRR*
			DM1	10	LRR, death	Generalised gamma	TP2 Osi : DF to DM1*
	Placebo	343	LRR	61	DM1, death	Log-normal	TP1 AM : DF to LRR*
			DM1	78	LRR, death	Generalised gamma	TP2 AM: DF to DM1*
CancerLinQ[64]	N/a	[redacted]	DM1	[redacted]	Death	Log-normal	TP4 (both groups): LRR to DM1
FLAURA[63]	Osimertinib	279	TTD (DM2 proxy)	NR	Death	Weibull	TP6 AM: DM1 to DM2 TP6 Osi: DM1 re-treat to DM2‡
	Osimertinib - post-TTD	205	Death	NR	N/a	Weibull	TP8 AM: DM2 to dead TP8 Osi : DM2 re-treat to dead
	Pooled arms	556	Death	11	TTD (DM2 proxy)	Exponential	TP7 Osi: DM1 to dead TP7 Osi: DM1 re-treat to dead TP7 AM: DM1 to dead
	Erlotinib/gefitinib†	277	TTD (DM2 proxy)	NR	Death	Weibull	TP6 Osi: DM1 to DM2
	Erlotinib/gefitinib - post TTD†	259	Death	NR	N/a	Weibull	TP8 Osi: DM2 to dead
General population life tables[40]	N/a	N/a	Death	N/a		N/a	TP3 and TP5 (both groups)

N - number; Osi - osimertinib; AM - active monitoring; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; TTD - time to treatment discontinuation; NR - not reported in the CS

** The company's model applies an assumption whereby the predicted probabilities of transitioning from DF to LRR and DM1 in both treatment groups are reduced by 95% after 5 years*

† Outcomes for the TKI arm in FLAURA are assumed to reflect outcomes for chemotherapy in the company's economic model

‡ The company's model includes an error whereby outcomes for patients re-treated with osimertinib are assigned the risk of transitioning from DM1 to DM2 from the TKI control arm of FLAURA (see Section 5.3.4)

Summary of survival modelling methods

For each transition, the company fitted six standard parametric survival models. These included: the exponential; Weibull; log-logistic; log-normal; generalised gamma and Gompertz survival distributions. The 2-parameter gamma model and generalised F distributions were not considered in the analysis. In addition, more flexible models such as mixture-cure models and restricted cubic spline 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 models were 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 ERG notes that care should be taken to avoid interpreting 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 CS[1] states that the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to evaluate goodness-of-fit, but also cite a paper on multistate modelling by Williams *et al*.[84] which states that AIC is not an appropriate measure in the competing risk setting. In fact, the company used a variety of methods and criteria to assess the models and to choose their preferred model in each case. These included the consideration of: visual fit of the fitted models to the Kaplan-Meier plots; statistical goodness-of-fit (AIC and BIC), and 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, a key criterion used for TP1 and TP2 was consistency with an assumption of cure.

Cure assumption

As described in Section 5.2.3, 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; patients remaining in this health state are assumed to have the same mortality risk as that of 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[37] (TP1 and TP2). The plots of model-predicted probabilities of experiencing distant relapse and loco-regional recurrence, as shown in Figure 8 and Figure 9, reflect

the fitted parametric survival model predictions and do not show the impact of this structural cure assumption.

The company's cure assumption was informed by advice provided by six UK clinicians who supported the following assertions:

(i) Patients are at greatest risk of recurrence between 18 and 24 months following surgical resection

(ii) Patients are typically discharged at 5 years if no recurrence has occurred and can be considered functionally cured

(iii) It can be reasonably assumed that survival will subsequently be similar to that for the general population

(iv) The significant DFS benefit with osimertinib in the ADAURA trial[37] (see Section 4.2.3) 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 also drawn from the ADAURA trial[37] in that, compared with the control group, the 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 mixture-cure models to data from the ANITA trial (adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA)[85] which suggested curative potential for a proportion of patients, albeit in a separate study to ADAURA (estimated cure fractions ranged from 0.16 to 0.31; further details are provided in CS[1] Section B.3.3.3.1).

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[37] with competing events (distant recurrence and death) censored. Kaplan-Meier plots of the data used in the analysis are shown in CS[1] Figure 19. The six candidate survival distributions were fitted separately to the data for each arm and were plotted against the observed Kaplan-Meier functions with extrapolations to 40 years (see Figure 8). AIC and BIC statistics for the fitted models are presented in Table 22.

The company stated that visual goodness-of-fit and plausibility of the extrapolations were used as criteria for selecting the preferred survival function. The ERG notes that the primary determining factor for model selection was the compatibility of the functions with the adopted cure assumption (95% of patients cured at 5 years). The log-normal and generalised gamma distributions were deemed by the company to be compatible with this assumption, with the other models featuring overly pessimistic

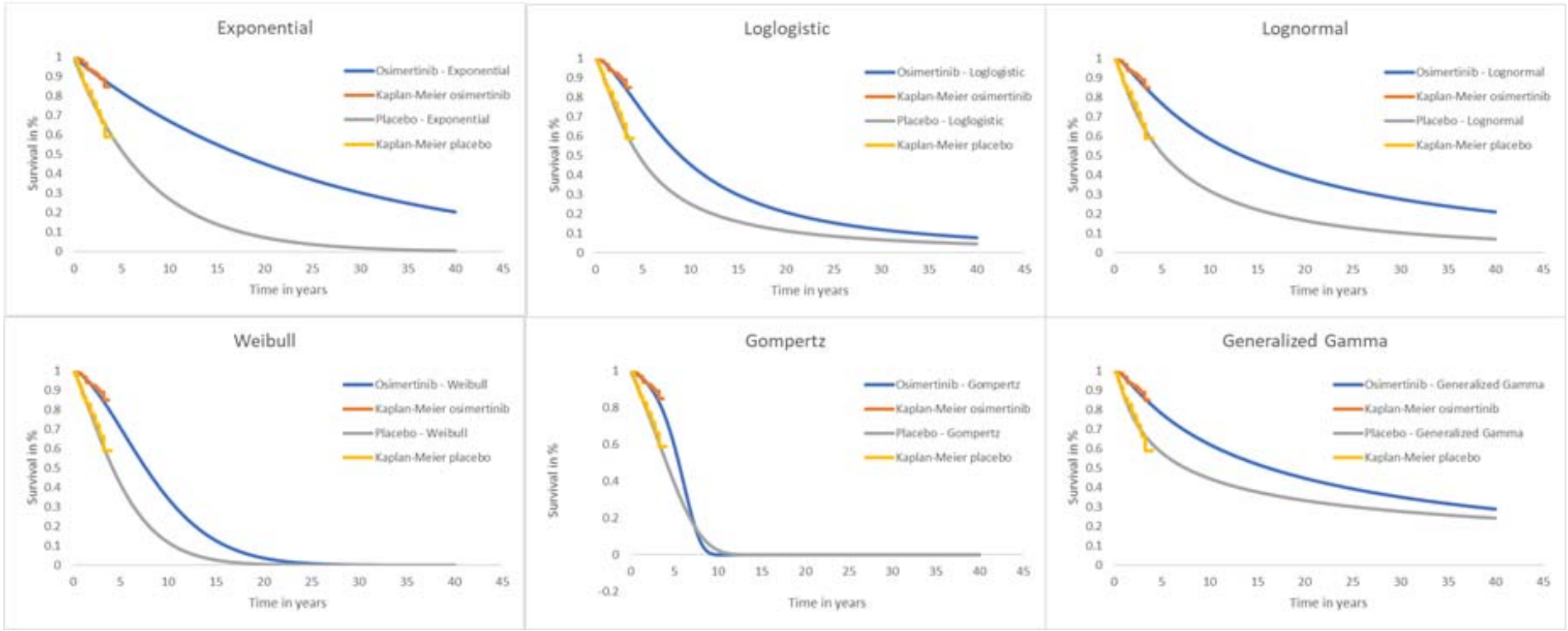
long-term extrapolations. The log-normal distribution was selected for inclusion in the company's base case as it has a lower AIC and BIC in both arms (see Table 22) and because the expected treatment effect between the arms is maintained. The ERG notes that this latter issue relates to the extrapolation rather than goodness-of-fit and is based on the assumption that the treatment effect for osimertinib versus placebo will be maintained beyond the observed period of the trial. The generalised gamma distribution was included in the company's scenario analysis.

Table 22: AIC and BIC statistics, DF to LRR (TP1), ADAURA

Model	Osimertinib		Placebo (Active monitoring)	
	AIC	BIC	AIC	BIC
Exponential	314.32	318.15	685.82	689.66
Weibull	310.66	318.32	683.06	690.73
Log-logistic	310.55	318.20	681.99	689.67
Log-normal (base case)*	**309.89**	**317.54**	**678.46**	**686.13**
Gompertz	312.82	320.47	686.36	694.03
Generalised gamma*	311.86	323.33	679.09	690.60

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; DF - disease-free; LRR - loco-regional recurrence
Values shown in bold indicate best fitting models. Asterisks indicate models which were considered to be potentially plausible by the company

Figure 8: Observed Kaplan-Meier and modelled survival distributions, DF to LRR (TP1), ADAURA (reproduced from CS, Figure 21)



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[37] with competing events (loco-regional recurrence and death) censored. Kaplan-Meier plots of the data used in the analysis are shown in CS[1] Figure 22. The six candidate survival distributions were fitted separately to the data for each arm and were plotted against the observed Kaplan-Meier functions with extrapolations to 40 years (see Figure 9). AIC and BIC statistics for the fitted models are presented in Table 23.

The log-normal and generalised gamma distributions were deemed to be consistent with the cure assumption, with the remaining four distributions predicting no long-term survival (i.e. no patients remaining free of distant metastases) in one or both of the arms. The log-normal distribution had the best statistical fit to the osimertinib arm data, whilst the generalised gamma model had a better fit to the placebo arm data (see Table 23). However, the log-normal models were considered to be clinically implausible due to the survival functions for the arms crossing (at around 22 years post-randomisation). The generalised gamma was therefore selected for inclusion in the company's base case analysis. No alternative survival distributions for TP2 were considered in the company's scenario analyses.

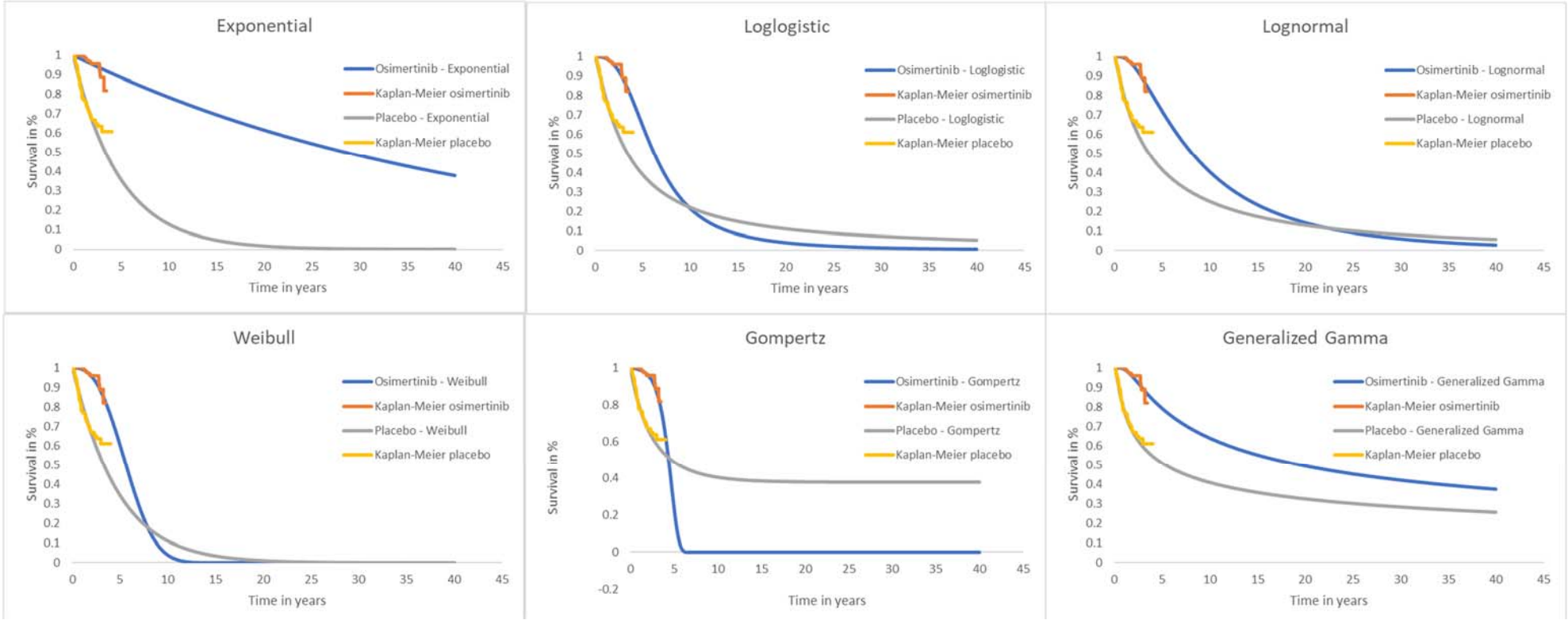
Table 23: AIC and BIC statistics, DF to DM1 (TP2), ADAURA

Model	Osimertinib		Placebo (active monitoring)	
	AIC	BIC	AIC	BIC
Exponential	206.01	209.84	991.11	994.95
Weibull	194.19	201.84	992.91	1000.58
Gompertz	196.52	204.18	990.13	997.81
Log-normal	**193.49**	**201.14**	979.52	987.2
Log-logistic	194.17	201.82	987.45	995.12
Generalised gamma (base case)*	195.16	206.64	**974.42**	**985.93**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; DF - disease-free; DM1 - first-line treatment for distant metastases

Values shown in bold indicate best fitting models. Asterisks indicate models which were considered to be potentially plausible by the company

Figure 9: Observed Kaplan-Meier and modelled survival distributions, DF to DM2 (TP2), ADAURA (reproduced from CS, Figure 24)



TP3: Disease-free to dead

Owing to the immaturity of the data from ADAURA,[37] the transition from DF to dead was modelled using age- and sex-matched general population life tables.[40]

TP4: Loco-regional recurrence to first-line treatment for distant metastases

Due to immaturity of the ADAURA trial data,[37] the company was unable to use this source to model the transition from LRR to DM1. Instead, data from CancerLinQ[64] on [redacted] 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. Kaplan-Meier plots of the data used in the analysis are shown in CS[1] Figure 25. The ERG assumes that the competing event of death was censored, although this is not explicitly stated in the CS. The six candidate distributions were fitted to the available individual patient data (IPD); the resulting parametric survival models were plotted against the observed Kaplan-Meier functions with extrapolations to 40 years (see Figure 10). AIC and BIC statistics for the fitted models are presented in Table 24.

The exponential and Weibull distributions were ruled out by the company on the basis of poor fit to the tail of the Kaplan-Meier plot as assessed visually (although the ERG notes that 95% CIs are not shown and numbers are small). The CS[1] refers to the use of external data to inform model selection for this event, but the company's clarification response[16] (question B12) notes that this was an error and that no external data exist. The Gompertz and generalised gamma models were also excluded *"because of their optimistic long-term estimates, which are unrealistic for patients at this stage."*[1] Whilst it is not entirely clear from the CS, the ERG presumes that the company is referring to the long-term extrapolations, rather than the end of the observed period (3-4 years). The remaining log-normal and log-logistic models provide a very similar visual fit to the observed data; the log-normal was chosen for the base case due to its markedly better statistical fit as judged by AIC and BIC. The log-logistic model was included in the company's scenario analysis.

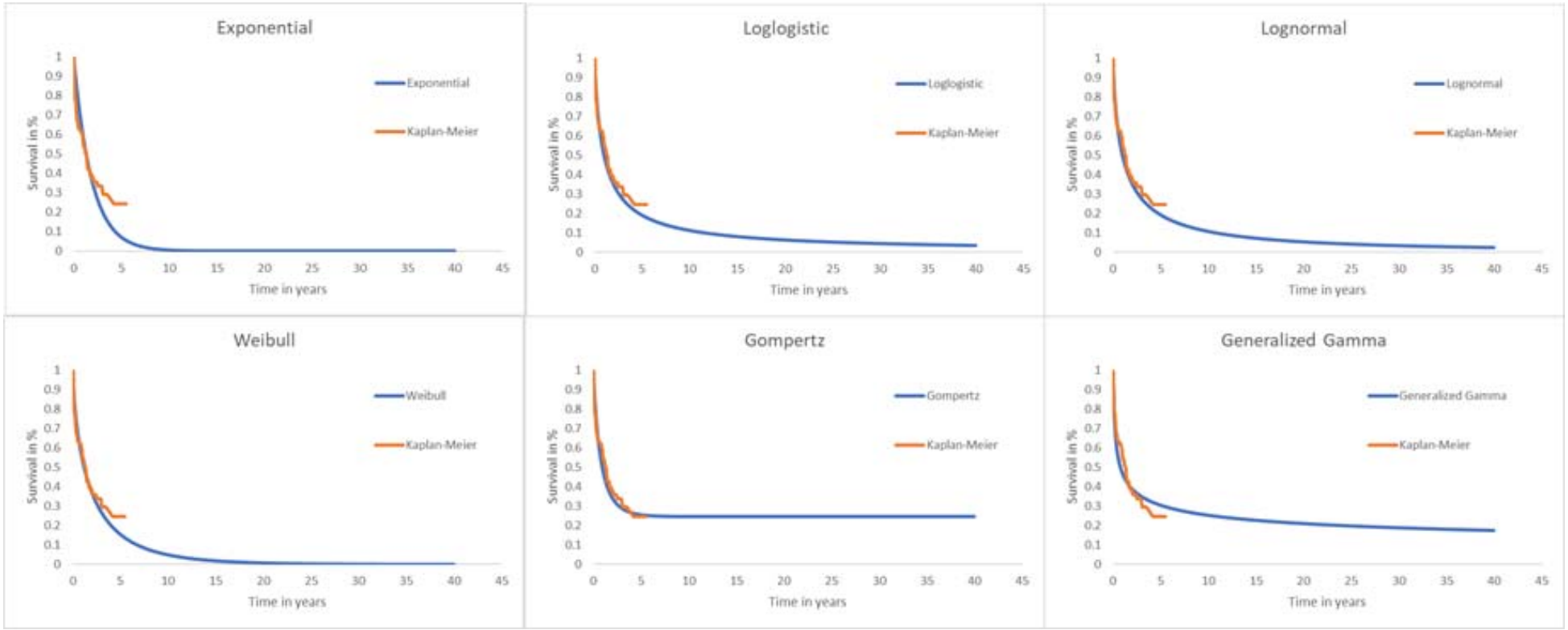
Table 24: AIC and BIC statistics, LRR to DM1 (TP4), CancerLinQ

Model	AIC	BIC
Exponential	447.83	450.4
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	**422.3**	**430.03**

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases

Values shown in bold indicate best fitting models. Asterisks indicate models which were considered to be potentially plausible by the company

Figure 10: Observed Kaplan-Meier and modelled survival distributions, LRR to DM1 (TP4), CancerLinQ (reproduced from CS, Figure 26)



TP5: Loco-regional recurrence to dead

Owing to the immaturity of the data and the lack of relevant events in ADAURA,[37] as well as a similar lack of events in the CancerLinQ dataset,[64] this transition was based on general population life tables.[40] The hazard is therefore the same as that used for TP3 (DF to death). The CS[1] (page 95) 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 ERG 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

There are two cases of this transition: (i) where DM1 includes re-treatment with osimertinib and (ii) where DM1 does not include re-treatment. The data for these transitions were taken from the FLAURA trial.[63] The CS[1] states that the Kaplan-Meier data were used, but the ERG assumes that IPD were used. Due to greater data maturity and for consistency with treatment costs, data on time to treatment discontinuation (TTD) for first-line treatment was used instead of progression-free survival (PFS) on the basis that the former is a reasonable proxy for the latter. The competing event of death was censored. Kaplan-Meier plots of the data used in the analysis are shown in CS Figure 27. The six candidate survival distributions were fitted separately to the data for each arm and were plotted against the observed Kaplan-Meier functions with extrapolations to 40 years (see Figure 11). AIC and BIC statistics for the fitted models are presented in Table 25.

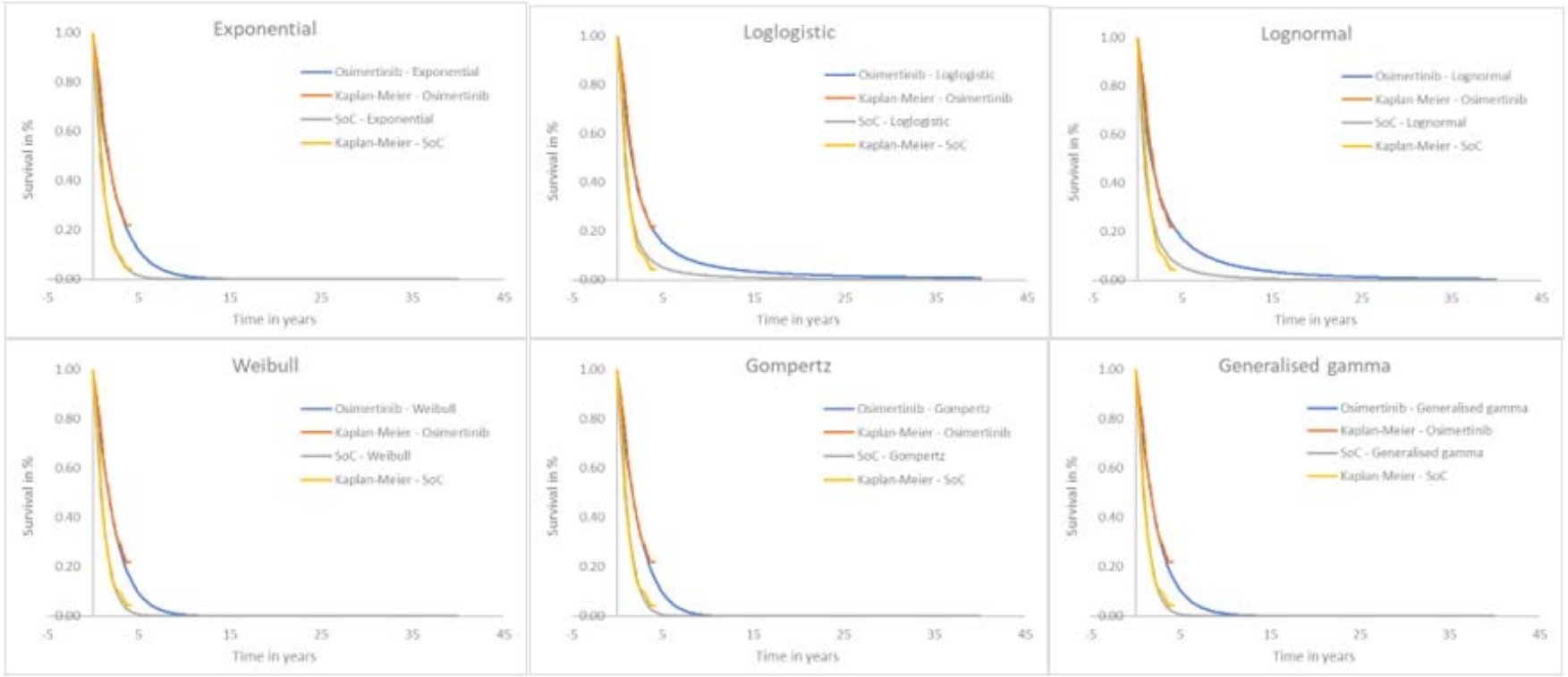
The log-normal and log-logistic models were excluded as the associated extrapolations were considered to be too optimistic to be clinically plausible, although the CS[1] does not provide any reasoning to support this assertion. The company's clarification response[16] (question B13) states that the log-logistic and log-normal parametric distributions were deemed to overfit the tail of the EGFR-TKI control arm of the FLAURA trial and that given the maturity of data from this study, the choice of the parametric distribution does not significantly affect the ICER (CS, Section B.3.8.3). The four remaining survival distributions were considered to be very similar; the Weibull model was selected for inclusion in the base case as it had the best statistical fit based on the AIC and BIC values (see Table 25). The generalised gamma model was included in the company's scenario analysis. The ERG notes that the company's economic model erroneously applies the parametric survival model for erlotinib/gefitinib for the transition from DM1 to DM2 for patients who are re-treated with osimertinib; this has been corrected in the company's updated model (see Section 5.3.5).

Table 25: AIC and BIC statistics, DM1 to DM2 (TP6), FLAURA

Model	Osimertinib		Erlotinib/gefitinib	
	AIC	BIC	AIC	BIC
Exponential*	1867.24	**1870.87**	1951.26	1954.89
Weibull (base case)*	**1865.18**	1872.45	**1945.91**	**1953.15**
Gompertz*	1868.25	1875.51	1950.2	1957.45
Log-normal	1886.11	1893.37	1999.94	2007.19
Log-logistic	1865.74	1873	1966.6	1973.85
Generalised gamma*	1866.59	1877.48	1947.9	1958.77

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases
Values shown in bold indicate best fitting models. Asterisks indicate models which were considered to be potentially plausible by the company

Figure 11: Observed Kaplan-Meier and modelled survival distributions, DM1 to DM2 (TP6), FLAURA (reproduced from CS, Figure 29)



TP7: First-line treatment for distant metastases to dead

For the transition from DM1 to dead, the same parametric survival model was used for the treatment group (with and without re-treatment) and the control group. This model was fitted to pooled data on time-to-death from both arms of FLAURA[63] (censored for treatment discontinuation). Kaplan-Meier plots of the data used in the analysis are shown in CS[1] Figure 30. The six candidate survival distributions were fitted to the data and were plotted against the observed Kaplan-Meier functions with extrapolations to 40 years (see Figure 12). The survival function for the general population was also included in the plots. AIC and BIC statistics for the fitted models are presented in Table 26.

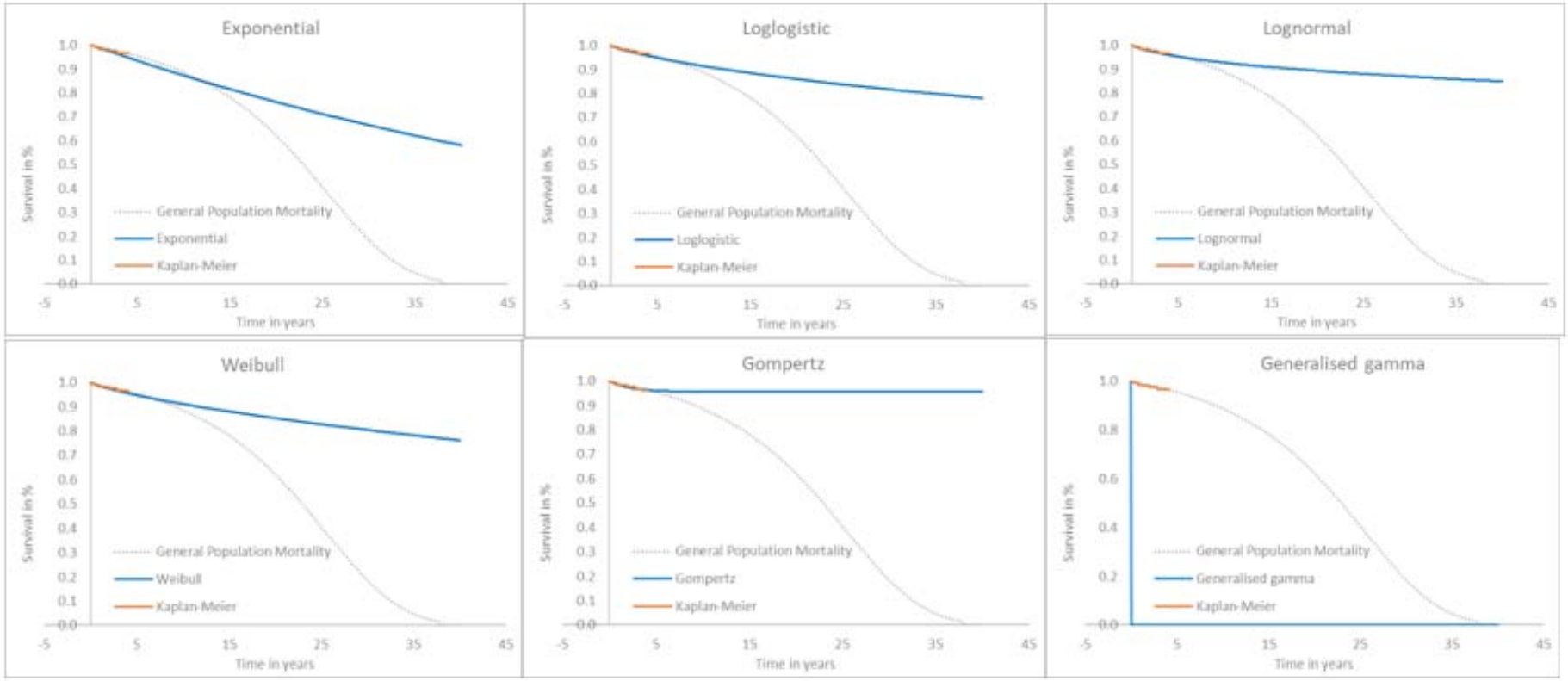
The exponential model had the best statistical fit based on AIC and BIC and was the only model that the company considered to be clinically plausible, as the other functions all generated survival predictions which were better than those for the general population.[40] No alternative survival distributions for TP7 were considered in the company's scenario analyses.

Table 26: AIC and BIC statistics, DM1 to dead (TP7), FLAURA (both arms pooled)

Model	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	176.92	189.88

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; DM1 - first-line treatment for distant metastases
Values shown in bold indicate best fitting models. Asterisks indicate models which were considered to be potentially plausible by the company

Figure 12: Observed Kaplan-Meier and modelled survival distributions, DM1 to dead (TP7), FLAURA - pooled arms (reproduced from CS, Figure 31)



TP8: Second-line treatment of distant metastases (DM2) to dead

Transitions from DM2 to dead (TP8) were estimated using data from FLAURA.[63] There are no competing risks for this transition as the only remaining event is death. Kaplan-Meier plots of the data used in the analysis are shown in CS[1] Figure 32. The six candidate survival distributions were fitted separately to the data for each arm and were plotted against the observed Kaplan-Meier functions with extrapolations to 40 years (see Figure 13**)**. AIC and BIC statistics for the fitted models are presented in Table 27.

The first criterion used to judge the models was comparison against external data: a publication reported by the US Surveillance Epidemiology and End Results (SEER) Program Cancer Statistics Review with a long-term dataset (2010–2016) reported a 5-year survival probability of 6.9% for distant metastases stage NSCLC patients.[86] Based on a comparison against this, the log-logistic and log-normal models were ruled out as they predicted cumulative probabilities of survival which were greater than 10% at 5 years. The Gompertz model was ruled out because it predicted substantial long-term survival beyond the 40-year time horizon. The exponential model was ruled out as it was considered to be too pessimistic, although the basis for this judgement by the company is not provided in the CS[1]. The distributions that estimated a 5-year cumulative survival probability for the placebo arm that the company considered plausible were the Weibull (placebo arm: 4.5%, osimertinib arm: 9.9%) and generalised gamma (placebo arm: 3.5%, osimertinib arm: 10.8%). Based on statistical fit (AIC and BIC), the Weibull distribution was selected for inclusion in the company's base case. The generalised gamma distribution was included in the company's scenario analysis.

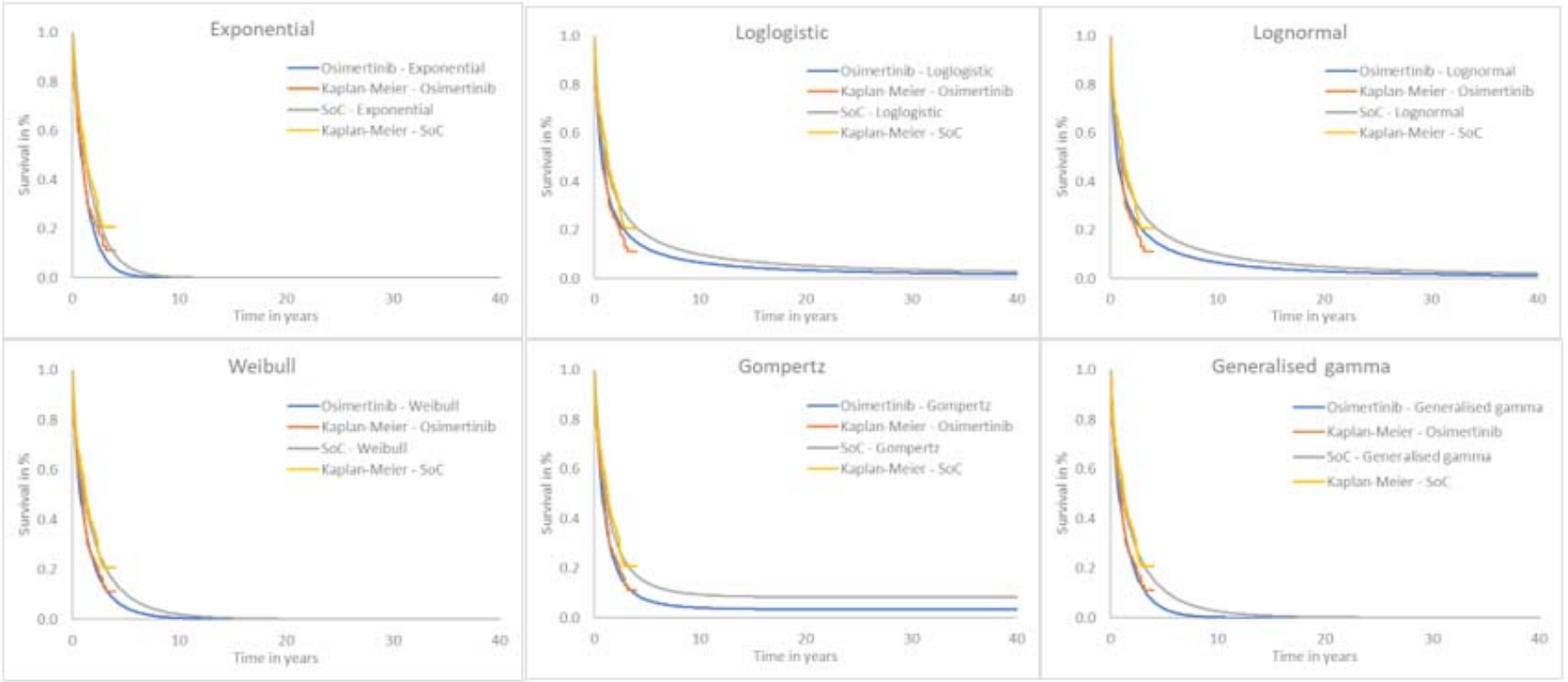
Table 27: AIC and BIC statistics, DM2 to dead (TP8), FLAURA

Model	Osimertinib		Erlotinib/gefitinib	
	AIC	BIC	AIC	BIC
Exponential	1118.4	1121.73	1329.18	1332.73
Weibull (base case)*	**1106.9**	**1113.55**	**1316.81**	**1323.93**
Gompertz	1114.31	1120.96	1323.71	1330.83
Log-normal	1125.08	1131.72	1324.37	1331.48
Log-logistic	1117.82	1124.47	1322.66	1329.78
Generalised gamma*	1108.51	1118.48	1318.73	1329.4

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; DM2 - second-line treatment for distant metastases

Values shown in bold indicate best fitting models. Asterisks indicate models which were considered to be potentially plausible by the company

Figure 13: Observed Kaplan-Meier and modelled survival distributions, DM2 to dead (TP8), FLAURA (reproduced from CS, Figure 34)



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,[37] whereas utility values for the DM1 and DM2 states were based on FLAURA[63] and Labbé *et al*.[72] These are described in more detail below.

Health utility values applied in DF and LRR health states

The ADAURA trial[37] 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.[1] The company's clarification response[16] (question A7) highlights that 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*.[87] 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). Observations with missing data from ADAURA were excluded, although the CS[1] notes that [redacted]

The mapped data from ADAURA are summarised in Figure 14. As shown in the figure, the mapped EQ-5D-3L utility estimates were generally high (utility ≥[redacted]) at all timepoints and were similar between the two treatment groups.

Figure 14: Mean EQ-5D-3L in ADAURA - all observations (reproduced from CS, Figure 39)

[redacted]

The company then 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 [redacted] patients in the osimertinib group and [redacted] patients in the placebo group of ADAURA.[16, 37] 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 28. The model predicts a mean utility excluding AEs of [redacted]. This utility value is applied in both the DF and LRR states of the company's base case model.

Table 28: Final RMME model applied in company's base case (adapted from CS, Table 34)

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

SD - standard deviation; AE - adverse event

As part of their clarification response[16] (question B16), the company also undertook a complete-case analysis. The results of this model were similar to the company's preferred model and are not reproduced here.

Health utility values applied in DM1 and DM2

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-positive NSCLC).[29] Within this appraisal, EORTC QLQ-C30 data collected in the FLAURA trial[63] were mapped to the EQ-5D-3L using a function reported by Young *et al*.[88] 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.*[72]). 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 29. All health state utility values were adjusted for age using Ara and Brazier.[71]

Table 29: Utility values applied in the company's model

Health state	Mean utility	SE	Source
DF	[redacted]	0.018	ADAURA[37] (SF-36 mapped to EQ-5D-3L). The same utility value is assumed for both DF and LRR states
LRR	[redacted]	0.018	
DM1	0.794	0.0069	FLAURA[63] (EORTC QLQ-C30 mapped to EQ-5D-3L).
DM2	0.640	0.03	Labbé *et al.*[72] (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

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.*[73] and NICE TA653.[34] The study reported by 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[34] (osimertinib for treating EGFR T790M mutation-positive advanced NSCLC) appear to be based on an analysis of the AURA3 trial.[89] Estimates of the frequency of Grade ≥3 AEs were taken from ADAURA.[37] Based on the AE frequencies and their estimated disutilities, the model applies QALY losses of -0.0022 and -0.0001 in the adjuvant osimertinib and active monitoring groups, respectively. These are applied in the first model cycle only.

Table 30: 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.*[73]	0.90%	0.00%	ADAURA[37]
Decreased appetite	-0.05	-0.0025	TA653[34] (AURA3[89])	0.60%	0.00%	
Diarrhoea	-0.0468	-0.0023	Nafees *et al.*[73]	1.80%	0.30%	
Stomatitis*	-0.05	-0.0025	TA653[34] (AURA3[89])	1.50%	0.00%	

AE - adverse event; SE - standard error; TA - Technology Appraisal
** Assumed to be the same as decreased appetite*

Resource use and costs

The model includes costs associated with: (i) drug acquisition and administration (adjuvant and downstream treatments); (ii) monitoring costs; (iii) disease management; (iv) management of AEs; (v) EGFR mutation testing and (vi) end-of-life care. The costs applied in the original model are summarised in Table 31; these are described in further detail in the subsequent text. It should be noted that several of the company's costing assumptions have been modified slightly in the updated version of the company's model submitted following the clarification process (see Section 5.3.5).

Table 31: Summary of model costs per cycle

Cost component (per 28-day cycle, unless otherwise stated)	Adjuvant osimertinib	Active monitoring
Adjuvant treatment, acquisition costs†	Osimertinib: [redacted]	N/a
Adjuvant treatment, administration costs†	Osimertinib: £8.40	N/a
LRR drug acquisition costs	PDC plus radiotherapy: £18,956*	PDC plus radiotherapy: £18,956*
LRR drug administration costs	PDC: Initial cycle £503.01; subsequent cycles £451.19§	PDC: Initial cycle £503.01; subsequent cycles £451.19
DM1 drug acquisition costs	PDC (100% patients with distant relapse before 5 years, 50% patients after 5 years) £1,405.43* Osimertinib (50% patients with distant relapse after 5 years): [redacted]	Osimertinib (100% patients with distant relapse): [redacted]
DM1 drug administration costs	Not included for osimertinib PDC: Initial cycle £503.01; subsequent £451.19	Osimertinib: £8.40
DM2 drug acquisition costs	PDC (patients re-treated in DM1): £1,405.43* Docetaxel (patients not retreated in DM1): £106.46*	PDC: £1,405.43*
DF2 drug administration costs	Not included for PDC Docetaxel: Initial cycle £501.78; subsequent cycles £449.95	PDC: Initial cycle £503.01; subsequent cycles £451.19
Disease management DF	£241.89	£241.89
Disease management LRR	£487.64	£487.64
Disease management DM1	£655.47	£655.47
Disease management DM2	£655.47	£655.47
CNS metastases costs (once-only cost on progression to DM1)‡	£11,404.29	£11,404.29
CNS metastases disease management costs	£386.87	£386.87
EGFRm testing (once-only cost)	£208.98	£208.98
AE management costs (once-only)	£79.10	£9.41
End-of-life care (once-only)	£2,219.80	£2,219.80

LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; CNS - central nervous system; EGFRm - epidermal growth factor receptor mutation; PDC - pemetrexed plus cisplatin; N/a - not applicable

** Cost only applies in cycles in which treatment is given*

† Maximum treatment duration = 3 years

‡ Includes sterotactic radiotherapy and whole-brain radiotherapy

§ Subject to an error whereby cost calculations are only applied for the first 3 years since model entry in the osimertinib group

Drug acquisition costs

Drugs given as treatments in the adjuvant setting and for loco-regional recurrence and distant metastases are summarised in Table 32. All drugs are costed according to a 28-day cycle duration. Separate price discounts for osimertinib are available applied in the adjuvant and metastatic settings; all results presented in this report include both of these discounts.

Table 32: Drug acquisition costs included in the company's model, includes PAS and CAA discounts for adjuvant osimertinib and metastatic osimertinib

Drug	Admin. route	Dose per admin.	RDI	Criteria for discontinuation	Drug cost per 28 days' supply	Source
Adjuvant treatment						
Osimertinib	Oral	80mg (daily)	98.9%‡	Maximum 3 years, progression or death	[redacted]	BNF[74]
Drug treatment for LRR						
Pemetrexed	IV	500mg/m^2	100%	Maximum 3 model cycles,* progression or death	£1,391.67	BNF[74]
Cisplatin	IV	75mg/m^2	100%	Maximum 3 model cycles,* progression or death	£13.76	eMIT[75]
Drug treatments for distant metastases						
Osimertinib	Oral	80mg (daily)	98.9%‡	Progression or death	[redacted]	BNF[74]
Pemetrexed	IV	500mg/m^2	100%	Maximum 3.8 model cycles,† progression or death	£1,391.67	BNF[74]
Cisplatin	IV	75mg/m^2	100%	Maximum 3.8 model cycles,† progression or death	£13.76	eMIT[75]
Docetaxel	IV	75mg/m^2	100%	Maximum 3 model cycles* or death	£106.46	BNF[74]

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; CAA - Commercial Access Agreement

** Corresponds to four 21-day treatment cycles*

† Corresponds to five 21-day treatment cycle

‡ The company's model includes an error whereby RDI is included but is not applied and thus does not impact on the ICER

Drug acquisition costs - adjuvant treatments

The list price per pack of 30 x 80mg osimertinib tablets (30 days' supply) is £5,700. 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[37] (see Figure 15) 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. According to the CS,[1] the company had intended to apply an

RDI of 98.9% for osimertinib in both the adjuvant and metastatic settings, based on the FLAURA trial;[63] however, the ERG notes that this variable is not applied in the company's cost calculations and therefore does not affect the company's ICER (see Section 5.3.4). The active monitoring comparator group does not include any drug treatment costs unless the patient experiences disease relapse.

Figure 15: Time to treatment discontinuation, ADAURA (reproduced from company's clarification response, question B9)

Drug acquisition costs - treatments for loco-regional recurrence

Patients who develop loco-regional recurrence are assumed to receive three model cycles of PDC and 20 fractions of radiotherapy. The list prices for 500mg IV pemetrexed and 75mg IV cisplatin are £1,391.67 and £13.76 per cycle, respectively. The model assumes that vial sharing is permitted for both pemetrexed and cisplatin. The cost per fraction of radiotherapy (assumed to be intraluminal brachytherapy) was taken from the NHS Reference Costs 2018/19;[76] this is applied in addition to the drug costs shown in Table 32.

The company's model calculates the total cost of a complete course of chemoradiation (total cost = £56,867.50) and then spreads this cost across the mean time spent in LRR in each treatment group.

Given that the company's model directly estimates the probability of being in LRR after 1, 2 or 3 cycles, the rationale for spreading these costs across all cycles is unclear.

Drug acquisition costs (treatments for distant metastases)

The model assumes that all patients in the active monitoring group who develop distant metastases receive first-line osimertinib followed by second-line PDC (3.8 model cycles). Within the adjuvant osimertinib group, the model assumes that all patients who experience distant relapse within 5 years and 50% of those who relapse after 5 years receive first-line PDC (3.8 model cycles) followed by docetaxel (3 model cycles), whilst the remaining 50% are assumed to receive first-line osimertinib followed by PDC (3.8 model cycles). The assumption regarding the proportion of patients who would be re-treated reflects an assumption made by the company which was ratified by six clinical experts (see clarification response,[16] question B5). The model includes a price discount of [redacted] for osimertinib in the metastatic setting; the cost per pack including this discount is [redacted]. [redacted]. The cost of 75mg IV docetaxel is based on the list price of £106.46 per cycle. The costs of pemetrexed and cisplatin (PDC) are the same as those described above. Vial sharing is assumed to be permitted in the company's base case.

As with the LRR state, the costs of fixed duration treatments for metastatic disease are spread across the mean time spent in the DM1 and DM2 states. Given that the model directly estimates the probability of being in each distant metastasis state at each timepoint, the rationale for applying costs in this way is unclear.

Drug administration costs

Table 33 summarises the drug administration and monitoring costs applied in the company's model. The model assumes an administration cost of osimertinib of £8.40 per cycle, based on the costs of pharmacy dispensing from the Personal Social Services Research Unit (PSSRU).[77] No further monitoring costs for osimertinib are applied in the model.

Drug administration costs for chemotherapy regimens (PDC and docetaxel) 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 - 8mg per day; docetaxel - 16mg per day). The unit costs for outpatient attendances were taken from NHS Reference Costs 2018/19.[76] Premedication with dexamethasone costs were based on prices listed in the Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT).[75] Drug monitoring costs are applied in each cycle in which patients receive PDC and docetaxel; no costs are assumed for osimertinib. The model assumes that patients receiving PDC have liver function, renal function and full blood count tests whilst patients receiving docetaxel require only a full blood count. Unit costs were taken from NHS Reference Costs 2018/19.[76] The company's base case model does not include any costs associated with drug wastage.

Table 33: Drug administration and monitoring costs

Cost type	Component	Unit costs			Source
		Osimertinib	PDC	Docetaxel	
Administration costs per treatment (initial cycle)	Pharmacy dispensing	£8.40	-	-	PSSRU[77]
	Chemotherapy outpatient attendance	-	£371.00	£371.00	NHS Reference Costs 2018/19[76]
	Dexamethasone	-	£1.27	£2.54	eMIT[75]
Administration costs per treatment (subsequent cycle)	Pharmacy dispensing	£8.40	-	-	PSSRU[77]
	Chemotherapy outpatient attendance	-	£332.10	£332.10	NHS Reference Costs 2018/19[76]
	Dexamethasone	-	£1.27	£2.54	eMIT[75]
Monitoring costs per treatment cycle	Liver function test	-	£1.10	-	NHS Reference Costs 2018/19[76]
	Renal function test	-	£1.10	-	NHS Reference Costs 2018/19[76]
	Complete blood count	-	£2.79	£2.79	NHS Reference Costs 2018/19[76]
Total cycle cost per 28-day cycle (initial cycle)		**£8.40**	**£503.01**	**£501.78**	-
Total cycle costs per 28-day cycle (subsequent cycles)		**£8.40**	**£451.19**	**£449.95**	-

PDC - pemetrexed plus cisplatin; PSSRU - Personal Social Services Research Unit; eMIT - electronic Market Information Tool

Disease management costs

Table 34 summarises the per-cycle disease management costs assumed for each of the four alive health states in the company's model. Resource use data for each state were taken from the published LuCaBIS study of patients with resected IB-IIIA NSCLC during adjuvant chemotherapy and following loco-regional recurrence or distant metastases (Andreas *et al.*[14]). In the DF health state, the average resource use for patients on and off adjuvant chemotherapy in Andreas *et al* was used. Following 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 2018/19.[76] The company's model applies the same costs to the health states for both the intervention and comparator groups.

Table 34: Disease management resource use and costs applied in the company's model

Resource Type	Frequency per 28-day cycle			Unit cost	Total cost per 28-day cycle		
	DF	LRR	DM1/DM2		DF	LRR	DM1/DM2
Hospitalisation	0.069	0.120	0.207	£598.73	£41.31	£71.60	£123.93
Oncologist visits (subsequent)	0.086	0.635	0.609	£148.95	£12.77	£94.55	£90.78
Surgeon visits	0.151	0.184	0.149	£205.89	£30.99	£37.88	£30.78
Pulmonologist/ respiratory physician (subsequent)	0.153	0.239	0.115	£163.62	£24.97	£39.13	£18.81
Other specialist visit	0.146	0.230	0.149	£148.95	£21.73	£34.26	£22.27
Emergency room	0.065	0.120	0.161	£174.15	£11.29	£20.83	£28.04
CT scans	0.079	0.202	0.264	£103.61	£8.23	£20.97	£27.40
MRI	0.044	0.092	0.138	£204.35	£8.97	£76.32	£28.20
PET scans	0.046	0.092	0.230	829.61	£38.16	£47.87	£190.79
PET-CT scans	0.065	0.092	0.115	£520.37	£33.73	£7.58	£59.84
Ultrasound	0.069	0.092	0.149	£82.37	£5.68	£17.86	£12.31
Nuclear medicine studies	0.021	0.092	0.115	194.20	£4.06	£18.80	£22.33
Total cost	-	-	-	-	**£241.89**	**£487.64**	**£655.47**

DF - disease-free; LRR - loco-regional recurrence: DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; CT - computerised tomography; MRI - magnetic resonance imaging; PET - positron emission tomography

Additional disease management costs were included for a proportion of patients who develop distant CNS metastases (see Table 35). Estimates of the proportion of patients who experience CNS metastases were taken from the intervention and comparator arms of the ADAURA trial.[37] Estimates of the additional resources required to manage CNS metastases were taken from TA536;[78] unit costs were taken from NHS Reference Costs 2018/19[76] and the PSSRU.[77] 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 from the Royal College of Radiologists.[79] Unit costs for stereotactic radiotherapy were taken from NHS Reference Costs 2018/19, whilst the unit cost for whole-brain radiotherapy was based on TA536[78] and was inflated to 2019 prices using the NHS Cost Inflation Index (NHSCII).

Table 35: CNS metastases disease management costs applied in the company's model

CNS metastases cycle costs					
Resource Type	**Frequency per 28-day cycle**	**Unit cost**	**Total costs**	**Frequency source**	**Unit cost source**
GP visit	0.9	£39.00	£35.88	TA536[78]	PSSRU[77]
Consultant/ oncologist outpatient visit	0.5	£148.95	£80.50		NHS Reference Costs 2018/19[76]
Cancer nurse visit	1.4	£98.74	£136.25		
Full blood test	1.4	£2.79	£3.85		
Biochemistry	1.4	£1.10	£1.52		
CT scan	0.4	£115.19	£49.01		
MRI scan	0.3	£204.35	£65.79		
X-ray	0.5	£30.59	£14.07		
Total cost	**-**	**-**	**£386.87**	**-**	**-**
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	£3,084.42	£9,253.26	RCR report[79] and clinical opinion	NHS Reference Costs 2018/19[76]
Whole brain radiotherapy*	1	£4,302.06	£ 2,151.03		TA536 ERG report[90]
Total cost	**-**	**-**	**£11,404.29**	**-**	**-**

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 36 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;[37] only Grade 3/4 events that occurred in two or more patients in either treatment arm in the trial were included. Unit costs were based on NHS Reference Costs 2018/19.[76] 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.

Table 36: AE frequencies and costs

AE	**Frequency - adjuvant osimertinib**	**Frequency - active monitoring**	**Unit cost**	**Total cost- osimertinib**	**Total cost- active monitoring**
Paronychia	0.90%	0.00%	£1,509.22	£13.58	£0.00
Decreased appetite	0.60%	0.00%	£1,987.00	£11.92	£0.00
Diarrhoea	1.80%	0.30%	£1,396.32	£25.13	£4.19
Stomatitis	1.50%	0.00%	£853.18	£12.80	£0.00
ECG QT prolonged	0.90%	0.30%	£1,739.85	£15.66	£5.22
Total cost	**-**	**-**	**-**	**£79.10**	**£9.41**

AE - adverse event; ECG - electrocardiogram

EGFR mutation testing

The company's model assumes that all patients receiving osimertinib, either in the adjuvant or metastatic setting, will require an EGFR mutation test prior to starting treatment. The model assumes that patients re-treated with osimertinb do not require re-testing for EGFR mutations. The cost of the test was based on NICE Diagnostics Guidance 9 (DG9)[80] and was uplifted to current prices using Curtis *et al.*[77] The model applies a testing cost of £208.98 per patient receiving osimertinib. The ERG notes that around 10 patients will need to be tested in order to identify one patient with an EGFR mutation; hence, the costs included in the company's model are underestimated. This issue is discussed further in Section 5.3.4.

End-of-life care

The cost of end-of-life care was applied as a once-only cost of £2,219.80 to patients at the point of death. This estimate was based on the proportion of patients who require terminal care in either hospital, in a hospice or at home based on a published study by Brown *et al.*[81] Costs were based NHS Reference Costs 2018/19,[76] the PSSRU[77] and a report by Marie Curie Cancer Care.[82]

5.2.5 Model evaluation methods

The CS[1] presents a base case incremental cost-effectiveness ratio (ICER) for adjuvant osimertinib versus active monitoring based on point estimates of parameters. Results are also presented using the probabilistic version of the model, based on 1,000 Monte Carlo simulations. The distributions applied in the company's probabilistic sensitivity analysis (PSA) are summarised in Table 37. The results of the company's 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: discount rates; cure proportions and timepoints; re-treatment proportions and timepoints; alternative parametric survival distributions for parameters; the inclusion of a HR for the transition from DM1 to DM2 based on a published network meta-analysis (NMA);[91] alternative health state utilities and the exclusion of the cost of EGFR testing.

Table 37: Summary of distributions used in company's PSA

Parameter group	Parameter(s)	Distribution	ERG comment
Patient characteristics	Body surface area	Normal	-
	Start age	Fixed	This parameter is subject to uncertainty
	Proportion male	Fixed	This parameter is subject to uncertainty
Safety	AE frequency	Beta	SE assumed to be 10% of the mean
	AE duration	Fixed	-
Health state transitions	Transition probabilities	MVN	-
Efficacy	HR adjustment for DM1 to DM2	Fixed	This parameter is subject to uncertainty
Cure	Cure timepoint	Fixed	This is a structural assumption that is subject to uncertainty
HRQoL	Health state utilities	Beta	SE assumed to be 10% of the mean utility for DF and LRR states.
	AE disutilities	Beta	SE assumed to 5% of the mean
	Age-adjustment utility coefficients	Fixed	The model indicates a beta distribution is used, but this parameter is not included in PSA
Costs	Drug acquisition costs	Gamma	SE assumed to be 10% of the mean
	Drug administration costs	Gamma	
	Disease management costs	Gamma	
	Costs associated with AEs	Gamma	
	End of life care costs	Gamma	
	CNS metastases management	Gamma	
Resource use	Treatment duration (number of model cycles)	Gamma	SE assumed to be 10% of the mean
	Proportion receiving each treatment (drug share)	Beta	
	Proportions receiving CNS metastases costs	Fixed	These parameters are subject to uncertainty. However, uncertainty around CNS management costs is modelled

AE - adverse event; ERG - Evidence Review Group; SE - standard error; HR - hazard ratio; HRQoL - health-related quality of life; CNS - central nervous system; PSA - probabilistic sensitivity analysis; DFS - disease-free; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases

5.2.6 Company's model results

This section presents the results of the company's original submitted model for consistency with the CS.[1] The company's updated model, which was submitted as part of the company's clarification response,[16] addresses several errors identified by the ERG and includes other changes to the base case assumptions and additional functionality to explore further scenarios. The company's updated base case model and its results are summarised separately in Section 5.3.5. The ERG's exploratory analyses, which includes the correction of some further errors and exploration of other uncertainties, are presented in Section 5.4.

Company's central estimates of cost-effectiveness (original submitted model)

Table 38 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; the corresponding ICER is £10,911 per QALY gained. The deterministic version of the model indicates a higher ICER of £12,849 per QALY gained. As shown in Table 38, the difference between the deterministic and probabilistic ICERs relates to the QALY gains estimated by the model. In response to a request for clarification from the ERG[16] (question B31), the company isolated the source of this discrepancy to an error in the probabilistic sampling of age-adjusted utilities and corrected this within their updated model (see Section 5.3.5).

Table 38: 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]	**£10,911**
Active monitoring	[redacted]†	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£12,849**
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 ERG by modifying the company's VBA sub-routine for performing PSA

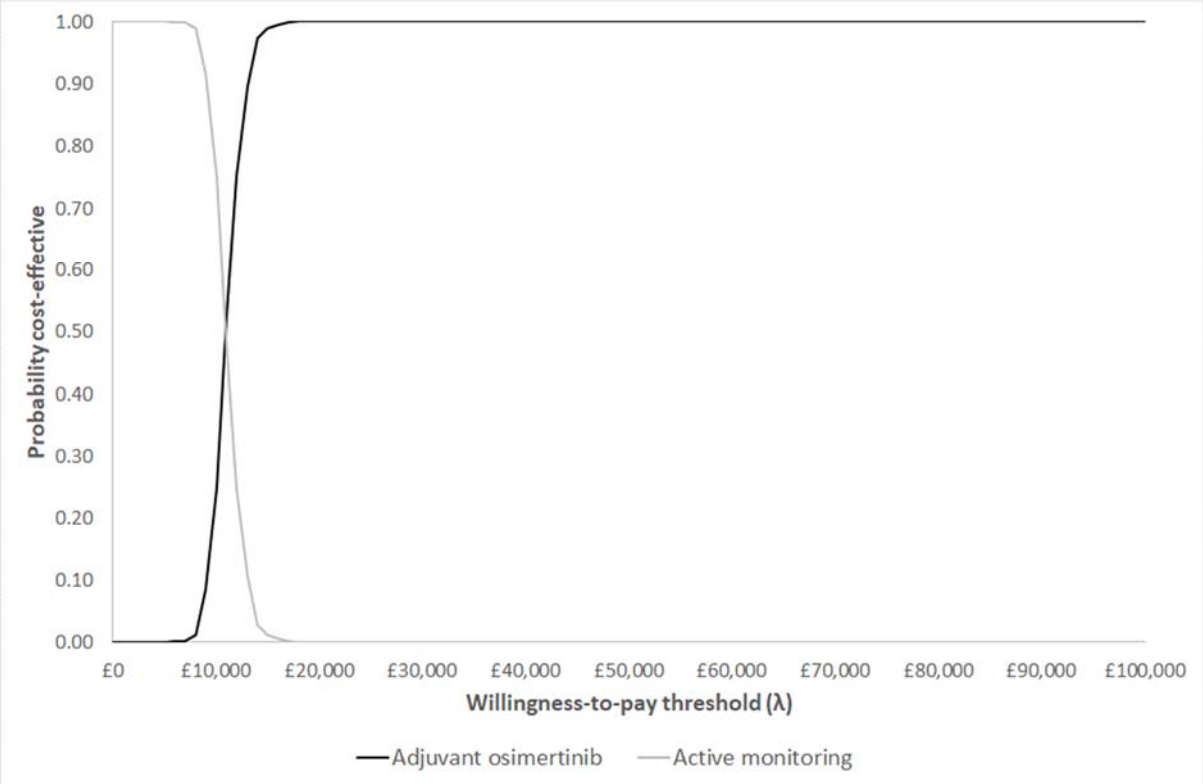
Company's PSA results (original submitted model)

The results of the company's PSA are presented in the form of a cost-effectiveness plane in Figure 16; the CEACs are shown in Figure 17. Assuming a willingness-to-pay (WTP) threshold of £20,000 per QALY gained, the company's model suggests that the probability that adjuvant osimertinib generates more net benefit than active monitoring is approximately 1.00.

Figure 16: Cost-effectiveness plane, adjuvant osimertinib versus active monitoring (generated by the ERG using the company's model)

[redacted]

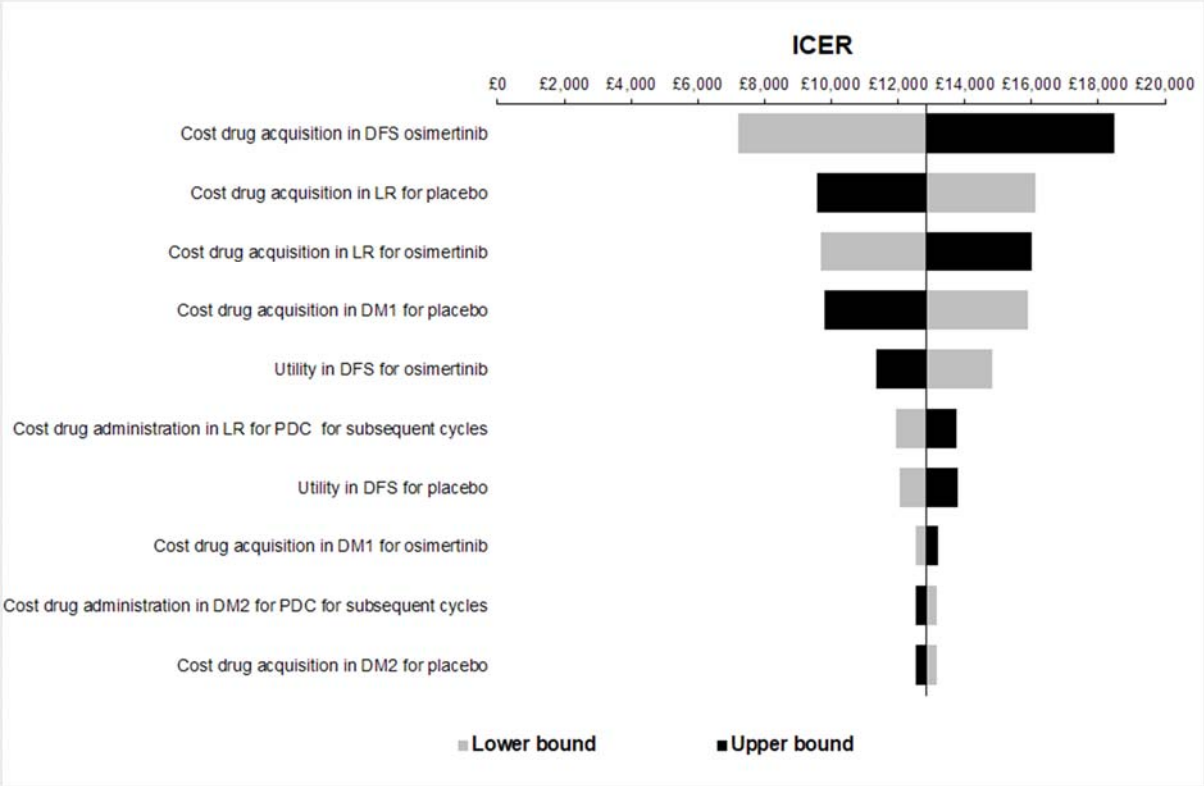
Figure 17: Cost-effectiveness acceptability curves, adjuvant osimertinib versus active monitoring (generated by the ERG using the company's model)



Company's DSA results (original submitted model)

Figure 18 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 sensitive to the acquisition cost of osimertinib, and to the costs for treatments given for loco-regional recurrence and for the first-line treatment of distant metastases. The ERG notes that the acquisition costs of osimertinib and PDC are not uncertain quantities and it is unclear why the company has included these in the DSA. Across all DSAs, the highest ICER reported for adjuvant osimertinib versus active monitoring is £18,478 per QALY gained.

Figure 18: Tornado diagram, adjuvant osimertinib versus active monitoring (generated by the ERG using the company's model)



Company's scenario analysis results

Table 39 presents the results of the company's scenario analyses. As shown in the table, the ICER is estimated to range from £9,147 per QALY gained (SA1: discount rates = 1.5%) to £14,713 per QALY gained (SA13: utilities from Andreas *et al,*[14] higher utility value in DM2).

Table 39: 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]	**£12,849**
SA1. Discount rates = 1.5%	[redacted]	[redacted]	[redacted]	**£9,147**
SA2. Cure timepoint 4 years	[redacted]	[redacted]	[redacted]	**£12,616**
SA3. Cure timepoint 6 years	[redacted]	[redacted]	[redacted]	**£13,694**
SA4. Cure percentage 90%	[redacted]	[redacted]	[redacted]	**£12,944**
SA5. Cure percentage 100%	[redacted]	[redacted]	[redacted]	**£12,805**
SA6. Cure timepoint 4 years with 1-year warm-up increasing 50% to 95% cure	[redacted]	[redacted]	[redacted]	**£12,502**
SA7. Retreatment timepoint 4 years	[redacted]	[redacted]	[redacted]	**£13,573**
SA8. Retreatment timepoint 6 years	[redacted]	[redacted]	[redacted]	**£12,597**
SA9. Osimertinib re-treatment percentage 40%	[redacted]	[redacted]	[redacted]	**£12,676**
SA10. Osimertinib re-treatment percentage 60%	[redacted]	[redacted]	[redacted]	**£13,023**
SA11. Second-best fit viable survival models: • TP1 (DF to LRR): generalised gamma • TP4 (LRR to DM1): log-logistic • TP6 (DM1 to DM2): generalised gamma • TP8 (DM2 to death): generalised gamma	[redacted]	[redacted]	[redacted]	**£14,457**
SA12. HR adjustment to DM1 (gefitinib vs. chemotherapy from Holleman *et al*. NMA[91])	[redacted]	[redacted]	[redacted]	**£12,649**
SA13. Utilities from Andreas *et al*, 2018[14] (DF=0.72; LRR=0.62; DM1 & DM2=0.67)	[redacted]	[redacted]	[redacted]	**£14,713**
SA14. Utilities from Andreas *et al*, 2018[14] (DF=0.72; LRR=0.62; DM1 & DM2=0.59)	[redacted]	[redacted]	[redacted]	**£14,138**
SA15. EGFR test cost excluded	[redacted]	[redacted]	[redacted]	**£12,821**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; SA - scenario analysis; DF - disease-free; LRR - loco-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; HR - hazard ratio; Inc. - incremental
** Undiscounted*

5.3 Critical appraisal of the company's economic analyses

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's original economic analysis and the underlying health economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[92, 93]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming 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.
- Examination of the correspondence between the company's executable model and its description in the CS.[1]
- Replication of the results of the company's base case analysis, PSA, DSAs and scenario analyses reported in the CS.
- Where possible, checking key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

5.3.1 Model verification by the ERG

Table 40 presents a comparison of the results of the deterministic version of the company's original model and the ERG's double-programmed model. As shown in the table, the ERG's results are very similar to those generated using the company's model. However, the ERG's double-programming exercise revealed a number of implementation errors and other conceptual issues; these are discussed in detail in Section 5.3.4. Many of these have been addressed within the updated version of the company's model submitted following the clarification process.

Table 40: Comparison of results generated using the company's original model and the ERG's double-programmed model, excludes correction of errors

Outcome	ERG's double-programmed model		Company's 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	**£12,845**		**£12,849**	

ERG - Evidence Review Group; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

5.3.2 Correspondence between model inputs and original source data

Where possible, the ERG checked the model input values against their original sources. The ERG found some minor discrepancies, as detailed below.

The company's model applies the acquisition cost for docetaxel from the BNF;[74] however, a lower price is available from eMIT[75] (BNF price = £51.00; eMIT price = £12.50).

Unit costs for health state resource use all apply weighted averages calculated from NHS Reference Costs.[76] However, CS[1] Table 46 only describes using weighted averages for hospitalisations, PET-CT scans and ultrasound scans. The CS does not describe the use of weighted averages or describe which exact unit costs are included in these. The ERG believes that some unit costs have been included which may not reflect clinical practice. For example, the model cost for subsequent oncology visits is based on the weighted average for consultant-led outpatient attendance for clinical oncology including: admitted and non-admitted; face-to-face and non-face-to-face; follow-up and first visits; multi-professional and single consultant-led attendances. A similar approach has also been used (and is not described in the CS[1]) for the costs of delivering chemotherapy drugs and administering radiotherapy fractions, in which the weighted average of inpatient, outpatient and other visits are included. One of the ERG's clinical advisors suggested that most radiotherapy is delivered in an outpatient setting, whilst most IV chemotherapy (i.e. PDC and docetaxel) is given in a day case setting.

Resource use for the management of CNS metastases were taken from TA536[78] and adjusted for baseline disease management costs and cycle length. In this appraisal, the percentage of patients requiring each resource item is reported alongside resource use. However, this is not applied in the company's model and instead it is assumed that 100% of patients will require each resource item.

The other model inputs appear to be consistent with their original sources. The ERG was unable to check the accuracy of the data used to inform the company's survival models or the utility analysis as IPD were not provided as part of the CS.[1]

5.3.3 Adherence of the company's model to the NICE Reference Case

The extent to which the company's economic analyses adhere to the NICE Reference Case[94] is summarised in Table 41.

Table 41: Adherence of the company's economic models to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The decision problem addressed by the company's economic model is in line with the final NICE scope.[22]
Comparator(s)	As listed in the scope developed by NICE	The company's model includes active monitoring as the sole comparator; this is consistent with the final NICE scope.[22] The ERG notes that the model assumes that all patients with distant metastases receive either osimertinib, PDC or docetaxel; this does not fully reflect current practice in England (see Section 3.3).
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The analysis adopts a direct NHS and PSS perspective, including health effects on patients.
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 based on the ADAURA trial:[37] this is the pivotal trial of osimertinib identified from the company's systematic review. Outcomes for treatments for LRR and distant metastases are based on data from CancerLinQ[64] and the FLAURA trial.[63] The ERG considers both of these data sources to be relevant to the decision problem.
Measuring and valuing health effects	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[37] (mapped from the SF-36), EQ-5D-3L estimates from FLAURA[63] (mapped from the EORTC QLQ-C30) and published EQ-5D-3L estimates from the literature (Labbé *et al*). Disutilities associated with AEs are based published literature (Nafees *et al*,[73] valued using the standard gamble technique) and NICE TA653 (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	

Element	Reference case	ERG comments
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 to estimated QALY gains.
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	The model includes differential pricing for osimertinib in the adjuvant and metastatic settings. Drug costs are valued at current prices. Other resource costs are valued using estimates from the NHS Reference Costs 2018/19[76] and the PSSRU.[77]
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.

ERG - Evidence Review 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

5.3.4 Key issues identified from the ERG's critical appraisal

This section presents a discussion of the main issues identified from the ERG's critical appraisal of the company's economic analysis, based on the original submitted model. These issues are summarised in Box 1, with a detailed discussion presented in the subsequent sections.

Box 1: Main issues identified from ERG's critical appraisal

(1) Presence of model errors
(2) Exclusion of other relevant downstream treatments for loco-regional and metastatic recurrence
(3) Issues relating to the company's model structure
(4) Uncertainty surrounding cure assumptions and impact on OS predictions
(5) Issues surrounding the company's survival analysis
(6) Use of TKI control arm of FLAURA to represent chemotherapy outcomes
(7) Effectiveness of re-treatment with osimertinib
(8) Uncertainty regarding representativeness of FLAURA to the target population following distant relapse
(9) Assumption of indefinite relative treatment effects for osimertinib in the metastatic setting
(10) Issues relating to utility values
(11) Issues relating to costs
(12) Comparison of observed and predicted DFS and OS
(13) Absence of subgroup analyses for patients with stage IB NSCLC

(1) Presence of model errors

The ERG identified a number of errors in the company's original submitted model: these are summarised in Table 42. With the exception of Items 17 and 18, these errors were identified before the ERG submitted the clarification letter. The company's clarification response[16] included an updated version of the model which addresses the majority of these errors (see Section 5.3.5).

Table 42: Summary of errors identified in the company's original submitted model

Item no.	Description of error
Model trace calculations	
1	The model trace is drawn from the "mid-cycle" calculations in the "TP matrix comp" worksheets. For the first model cycle, the model trace uses the uncorrected values (whereby all patients are in DFS at the beginning and the end of the cycle). This means that the first cycle is counted twice.
2	The model incorrectly uses 364 days per year rather than 365.25 days per year.
3	The model incorrectly uses 52 weeks in a year rather than 52.18 weeks per year.
4	The formulae applied in the DM1 sub-model for the comparator group refer to values for the transition from DM1 to dead which have not been adjusted for competing risks. The accompanying incident death calculations in the model are also incorrect.
Transition probabilities and survival	
5	The model assumes that a constant proportion of surviving patients are men in all model cycles, whilst simultaneously assuming that men and women have different death risks.
6	The model erroneously applies a cure proportion of 0.3167 (rather than 0.95) in the first cycle after the cure assumption is implemented.
7	Worksheets "TP Matrix Comp0", columns AG and AH. The competing risk adjustments in these columns include an =MAX() function which is not included in any of the other competing risk adjustments in either treatment group. This appears to be incorrect given these event risks are conditioned on time since state entry rather than time since model entry.
8	The approach used to adjust for competing risks conflates conditional survival probabilities and rates. In addition, the values for the first time interval are used in the first two cycles of the model.
9	Worksheet "STM_Surv". Within the adjuvant osimertinib re-treatment group, transition probabilities for DM1 to DM2 (column Q) are erroneously drawn from the TKI control arm of FLAURA.[63]
Costs	
10	The model calculates the costs of fixed duration treatments in LRR, DM1 and DM2 by spreading the total cost across the mean time spent in the health state. Given that these sub-models directly estimate the probability of remaining on treatment in each cycle, this approach is unnecessary and the company's approach leads to problems with discounting (see critical appraisal point [3]).
11	Treatment administration costs in LRR in the active monitoring group are not multiplied by the model trace and have a stopping rule applied at 3 years. This corresponds to worksheet "Trace Comp0", column AJ.
12	The cost of subsequent drug administration in DM1 in both treatment groups is incorrectly applied as £1.00.
13	Administration costs of osimertinib are not included for re-treated patients in DM1.
14	Worksheet "Trace Comp0", column AV. The model applies the administration cost of docetaxel to all patients who are re-treated with osimertinib in state DM2 (column N2). This should instead be applied to the "no-retreat" trace.
15	Drug administration costs for PDC in DM1 in the adjuvant osimertinib group are incorrectly applied to patients who are in the "re-treat" state (column L) and not to "no re-treat."
16	Drug administration costs of PDC are not applied to re-treated patients in DM2 in the adjuvant osimertinib group.
17	The probability of CNS metastases applied in DM1 is calculated using all relapses rather than distant metastases as the denominator
18	The RDI for osimertinib is not applied to the treatment cost calculations
HRQoL	
19	QALY losses associated with AEs are not divided by the number of cycles per year

TP - transition probability; TKI - tyrosine kinase inhibitor; DFS - disease-free survival; LRR - logo-regional recurrence; DM1 - first-line treatment for distant metastases; DM2 - second-line treatment for distant metastases; HRQoL - health-related quality of life; QALY - quality-adjusted life year; AE – adverse event

The company's updated model provided following clarification addresses all of these errors, except for items 5, 17 and 19. Overall, the impact of these errors on the ICER is small, reducing the company's original deterministic ICER from £12,849 to £11,136 per QALY gained (see Section 5.3.5, Table 45).

(2) Exclusion of other relevant downstream treatments for loco-regional and metastatic recurrence

As discussed in Section 2.2.5, the company's modelled pathway does not fully reflect the description of the treatment pathway in the CS.[1] In particular:

- All patients with loco-regional recurrence are assumed to be treated with chemoradiation. Surgery and single-modality radiotherapy are not included in the company's model. This is likely to overestimate costs for the comparator group as more patients experience loco-regional recurrence compared with the adjuvant osimertinib group.
- All patients who receive active monitoring and subsequently develop distant metastases are assumed to be treated with first-line osimertinib followed by second-line PDC. Other TKIs (erlotinib, gefitinib, afatinib and dacomitinib) are not included in the first- or second-line positions and other chemotherapy options such as the four-drug regimen of ABCP and nintedanib plus docetaxel are not considered in the second-line position. The ERG's clinical advisors believe that if adjuvant osimertinib were to receive a negative recommendation, the use of osimertinib as a first-line treatment for metastatic disease would increase in the future.
- Patients who receive adjuvant osimertinib may receive re-treatment with osimertinib as first-line treatment for distant metastases, followed by second-line PDC; those who are not re-treated are assumed to receive first-line PDC followed by docetaxel. Other chemotherapy options such as ABCP and nintedanib plus docetaxel are not considered in the second-line position. In addition, personal communication from NHSE indicated that if osimertinib was recommended in the adjuvant setting, TKIs would not be available as downstream treatments; hence re-treatment would not be permitted. This latter issue has only a minor impact on the ICER because the assumed 5-year timepoint for re-treatment with osimertinib coincides with the assumed timepoint at which the cure assumption is applied.
- All patients reaching DM1 and DM2 are assumed to receive active treatment. The ERG's clinical advisors suggested that between one-third and one-half of all patients with distant metastases will opt not to receive active therapy, either due to poor fitness or patient choice. However, they also commented that this would depend on which treatment was offered, as patients who are not fit enough to receive IV chemotherapy may be willing and able to take a well-tolerated oral tablet. As such, it is likely that the company's model overestimates health gains and costs associated with treatments for distant metastases in both treatment groups.

The company's base-case was updated as part of the clarification response[16] to include a proportion of patients with loco-regional recurrence (18%) being treated with single-modality radiotherapy, with the remainder receiving chemoradiation (question B24; see Section 5.3.5, Table 45). As part of their clarification response (questions A4 and B2), the company also presented separate additional scenario analyses which consider other TKIs in DM1 for the active monitoring group and which include ABCP in a proportion of patients in DM2 who have previously received a TKI as first-line treatment. The company's clarification response (question B1) also includes a separate scenario in which 10% of patients reaching DM1 and 25% of patients reaching DM2 are assumed not to receive active treatment and have lower costs (whilst retaining the same health outcomes as those assumed in the base case). The results of these scenario analyses are summarised in Section 5.3.5 (see Table 46). Notably, the scenario in which other TKIs are included in DM1 reduces the costs for the comparator group and thus increases the company's updated ICER, although this remains below £20,000 per QALY gained. The ERG notes that the joint impact of these alternative assumptions about the downstream treatment pathway has not been assessed within the company's clarification response.

(3) Issues relating to the company's model structure

Overall, the ERG believes that the company's model structure and modelling approach are generally appropriate. Patients who remain free from disease recurrence, those with loco-regional recurrence and those with distant metastases are expected to have different survival outcomes, different levels of HRQoL (although this is not fully reflected in the company's model) and will receive different treatments which affects costs. The ERG also considers the use of a semi-Markov approach, based on models fitted to IPD and adjusted for competing risks, to be appropriate. Given the limitations of the data available from ADAURA,[37] the ERG believes that the use of external data to inform the transitions for downstream events to be reasonable.

The ERG notes the following minor limitations associated with the company's model structure:

- Whilst the model structure allows for different utility values to be applied in the DF and LRR states, the company's base case applies the same value to both states. This is discussed further in critical appraisal point [10].
- The company's semi-Markov approach tracks the probability of remaining in each intermediate health state (LRR, DM1 and DM2) in each cycle. The costs of fixed duration treatments could therefore have been directly applied to those patients who entered the relevant health state within the previous 1, 2, 3 or 4 cycles. Instead, the company's model spreads the cost of these treatments over all model cycles, weighted by mean time spent in those states. This is unnecessary and will introduce a bias when discounting is applied. This issue is addressed within the company's updated model (see Section 5.3.5)

- The model applies the same utility value to all patients in the DM2 health state. However, it may have been more reasonable to partition the patient's remaining survival time after progression on first-line treatment in terms of whether they are progression-free on/after second-line treatment or not, as health utility is likely to be lower following progression. It is unclear whether the patients defined as "progressing" in Labbé *et al.*[72] were on treatment or if they had discontinued. However, the ERG notes that applying a lower overall mean utility for the DM2 state has only a minor impact on the ICER.

(4) Uncertainty surrounding cure assumptions and OS predictions

As discussed in Section 4.2.3, the available data on OS from ADAURA are immature, with only 29 deaths ([redacted]) recorded at the interim cut-off date.[37] Despite the limited OS data available, the company's original model predicts a substantial incremental OS gain of [redacted] years for adjuvant osimertinib versus active monitoring (see Table 38). This predicted OS gain is a function of all transitions included in the model, the majority of which are drawn from external data,[63, 64] and the company's cure assumption. This cure assumption accounts for a substantial proportion of this predicted OS gain for adjuvant osimertinib (incremental OS gain excluding cure = [redacted] years).

The ERG's clinical advisors commented that it is plausible that the observed advantage in DFS for osimertinib observed in ADAURA[37] could translate into an OS gain. However, they considered the survival gains predicted by the company's model to be *"very uncertain"* given the limited data available from ADAURA and noted that previous trials of TKIs given in the adjuvant setting had failed to demonstrate an OS advantage.[23-27] The clinical advisors further commented that the apparent separation of the model-predicted OS curves (shown later in Figure 21) may be *"too generous"* and suggested that a more modest difference between the curves might be expected, especially if a greater proportion of the active monitoring group go on to receive osimertinib in the metastatic setting.

Whilst the ERG's clinical advisors broadly agreed with the company's 5-year cure assumption for patients who undergo active monitoring, they suggested that it was feasible that adjuvant osimertinib may delay disease relapse, rather than prevent it.

As such, the ERG considers the company's modelled estimates of OS to be very uncertain.

(5) Issues surrounding the company's survival analysis

The general steps for model fitting and selection set out in TSD 14[83] can be summarised as follows:

(i) Consider whether joint survival models could be suitable across treatment arms.

(ii) Assess the suitability of parametric models using log cumulative hazard and analogous plots[95] and giving consideration to the observed hazards and clinical judgment about expected hazards and their relationship to the hazards assumed by the parametric models.
(iii) Fit a range of plausible candidate models
(iv) Assess the goodness-of-fit of the fitted models to the observed data using visual inspection and AIC and BIC statistics (although the TSD indicates that less emphasis should be placed on visual inspection)
(v) Assess the extrapolation of the survival models from the support of the observed data to the time horizon required by the proposed economic analysis, checking for clinical plausibility and consistency with relevant external data
(vi) Attempt to quantify uncertainty by supplementing the chosen base case model with a range of other plausible models.

Overall, the ERG considers that the company's approach to survival modelling is thorough and consideration is given to each of the points outlined above. However, there are some limitations in the company's analyses which are detailed below.

(i) Consideration of suitability of joint models

The company plotted the cumulative log hazard plot for each dataset modelled and used it together with a plot of the Schoenfeld residuals to assess evidence against making an assumption of proportional hazards (PH). The company did not investigate the possibility 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 data for each treatment arm for all events, thereby avoiding the PH assumption. The ERG 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.

(ii) Consider suitability of candidate models

The company did not state whether they used the log cumulative hazard plots to assess the suitability of the Weibull and exponential models and did not present or discuss similar plots that can be used for several of the other distributions. More importantly, the company did not discuss in any depth the clinically anticipated hazards and how these would evolve over time, nor did they present the observed hazards from the data within the CS.[1] There was therefore no consideration of whether the hazards assumed/implied by the chosen parametric survival models for each event are consistent with underlying beliefs about the nature of the true hazard. The company's clarification response[16] (question B10) further indicates that the nature of the hazard function for the candidate models was not used as part of their model selection process. The company's clarification response[16] (question C1) provided

plots of the observed hazard in the data underlying each survival model. The scale of the hazard axis on two of these plots (the osimertinib arm for TP1 and TP2) made interpretation difficult. However, the ERG found no indication of any conflict with the hazards assumed by the company's preferred survival models which were also broadly in keeping with the likely form of the hazards suggested by the ERG's clinical advisors.

(iii) Range of candidate models assessed

In each modelling analysis, the company fitted six standard parametric distributions: these included the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions. These six models are proposed as a minimum set in NICE TSD 14.[95] Other standard parametric survival models, including the 2-parameter gamma distribution and the generalised-F distribution, which is the most general and flexible of the standard parametric models, should have also been investigated. However, even this broader set of standard parametric survival models does not necessarily comprise a sufficient set of models for consideration. This is especially pertinent in instances in which the underlying hazard function for a given event is complex and cannot be adequately represented by standard models which allow for, at most, a single turning point. The ERG believes that more flexible distributions may have been appropriate, especially in the light of the company's belief that a substantial proportion of patients will achieve cure by a particular timepoint.

The company's reasons for not considering more flexible distributions such as restricted cubic splines and/or fractional polynomials were not clear. The CS[1] (page 78) states that *"a state transition modelling approach was considered instead of more flexible methods."* The ERG notes that there is no mutual exclusion between these two choices. The ERG considers that a more comprehensive range of models should have been considered, including the more flexible families of models, including restricted cubic splines and/or fractional polynomials. The ERG also notes that given that the economic model makes a strong assumption of cure, it may have been prudent to explore a mixture-cure modelling approach using the data from ADAURA;[37] this could allow the model to estimate cure fractions in each trial arm. Whilst the CS (page 78) suggests that the available data from ADAURA are not sufficiently mature to apply more flexible models, it is unclear whether this assertion is based on attempts to fit such models. As explained under Step (iv), it was difficult for the ERG to assess whether more flexibility was necessary on the basis of the information provided in the CS.

The ERG also notes that the company's rationale for using the same parametric model form for both arms of the ADAURA and FLAURA trials[37, 63] is not clear from the CS.[1] In the CS (page 78), the company states: *"TSD 14 states that the same parametric function should be used across both treatment arms where feasible as this ensures consistency and limits potential problems such as curves crossing over one another."* However, TSD 14 does not mention survivor functions crossing as a problem and

the ERG notes that survivor functions can often cross even when the same parametric form is used for both arms: this is evident in the company's survival analysis, despite the use of the same parametric form in each trial arm (see Figure 8 and Figure 9). Rather, TSD 14 states that *"fitting different types of parametric model (for example a Weibull for one treatment arm and a log normal for the other) to different treatment arms would require substantial justification, as different models allow very different shaped distributions"* and that fitting the same distribution is likely to be *"most sensible."*[83] Since the use of more flexible survival distributions has become widely accepted and used,[96] the recommendation to use the same distribution for both arms arguably becomes irrelevant as there will be sufficient flexibility for the hazards to take a different form in each arm. In the current context where a new drug has a marked effect on disease relapse compared to standard of care, it is likely that the hazards may take quite different forms in the two treatment arms and this possibility should be investigated.

(iv) Assess goodness-of-fit of the fitted models

In each model fitting process, the CS[1] states that visual inspection was used to assess goodness-of-fit. However, no specific comments are made in the CS on the basis of visual inspection, except in the case of the models for TP4 (LRR to DM1), where poor fit to the tail of the Kaplan-Meier survivor function is stated as partial support to the exclusion of two distributions (though the ERG notes that uncertainty in the Kaplan-Meier functions at this point are likely to make such statements unreliable).

The ERG also notes that whilst the CS[1] (pages 87, 90, 93, 98, 101 and 104) states that *"parametric distributions were assessed for their goodness of fit based on visual inspection",* the company actually appears to be referring to whether the long-term extrapolation is clinically plausible rather than goodness-of-fit *per se*. Goodness-of-fit relates specifically to the fit of the model to the observed data (i.e. the survivor functions in comparison, visually and statistically, to the KM functions); within the model selection process adopted by the company, goodness-of-fit was only used as a basis for selecting between any distributions that were deemed to be clinically plausible.

There is also some confusion over the role of AIC and BIC statistics. The company cite 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. It is unclear whether this is meaningful.

The ERG also notes that the company's plots of observed and modelled survival (see Figure 8 to Figure 13) do not include 95% CIs around the observed estimates. It is possible for some transitions (e.g. the placebo group in TP2 and TP4) the inclusion of such CIs may indicate that none of the models assessed are suitable. However, the company's clarifications response[16] (question C1) provided full Kaplan-Meier plot including uncertainty; the ERG was able to verify from visual inspection that the goodness-of-fit of the chosen survival functions was reasonable.

(v) 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, often using it as the primary criterion for model selection. In particular, the ERG notes that with respect to model selection for TP1 (DF to LRR) and TP2 (DF to DM1), the company gave more weight to consistency of extrapolations with the cure assumption, than to goodness-of-fit to the observed data. This is incongruous for several reasons:

(a) None of the fitted models appear to be consistent with the cure assumption;
(b) The cure assumption itself is uncertain, and;
(c) The extrapolations beyond the 5-year timepoint for many of the parametric survival models (except the Gompertz in TP1 and the Weibull and Gompertz in TP2) have a limited impact on the economic model predictions, as the cure assumption overrides the probabilities predicted by the parametric survival model, and the subsequent hazard (5% of the model-predicted hazard) is low. The ERG believes that selecting a parametric 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.

Notwithstanding the ERG's concerns regarding the limited set of models considered, the ERG believes that more weight should have been applied to both: (a) the fit of the models to the observed data for these transitions, and (b) the nature of the modelled hazard after the cure assumption is applied.

(vi) Sensitivity analyses

The company explored an alternative parametric survival model form for TP1, TP4, TP6 and TP8 in scenario analyses (see Table 39, Analysis S11). In the case of TP2, relaxation of the cure assumption or relaxation of the restriction that the same parametric model be used for both treatment arms would permit alternative models to be included, as outlined in Table 43. The ERG believes that this might allow for a more complete reflection of the impact of the true uncertainty in the assumptions to be quantified.

Table 43: Further scenario analyses proposed by the ERG where alternative survival models are considered potentially plausible for TP2 (DF to DM1)

Transition	Survival model	Justification
TP2	Log-normal model fitted to both arms	Statistical goodness of fit to the observed data and relaxation of cure criteria since it is also applied in the economic model subsequently.
TP2	Log-normal model fitted to treatment arm, generalised gamma model fitted to placebo arm	Statistical goodness of fit to the observed data and relaxing the condition that the same model is fitted to both arms.

TP - transition probability

(6) Use of TKI control arm of FLAURA to represent chemotherapy outcomes

The company's model uses data from the erlotinib/gefitinib control arm of the FLAURA trial[63] to estimate transition probabilities from DM1 to DM2 (TP6) and from DM2 to dead (TP8). Data from both the osimertinib and erlotinib/gefitinib control arms of FLAURA are used to inform the transition from DM1 to dead (TP7). However, the company's economic model assumes that these patients receive chemotherapy (PDC followed by docetaxel); as such, the model assumes that the risks of progression to next therapy and death for chemotherapy are equivalent to those for erlotinib/gefitinib. The ERG's clinical advisors did not consider this assumption to be appropriate, as erlotinib and gefitinib are more effective than chemotherapy in the metastatic setting. The assumption of equivalent outcomes for erlotinib/gefitinib and chemotherapy overestimates health gains for patients who are not re-treated with osimertinib in the metastatic setting, leading to a bias in favour of the adjuvant osimertinib group.

The CS[1] cites an NMA of thirteen trials of first-line TKIs in EGFRm-positive NSCLC reported by Holleman *et al.*[91] This study reported an HR on PFS for gefitinib versus chemotherapy of 0.43 (95% credible interval [CrI] 0.37, 0.49) and an HR for erlotinib versus chemotherapy of 0.36 (95% CrI 0.30, 0.43). Whilst the HR for gefitinib was applied to the TKI arm of FLAURA in the company's scenario analyses (see Table 39, Analysis S12), this adjustment was not included in the company's base case analysis. The ERG notes that because the company's model adopts a state transition approach which involves modelling each underlying transition, applying this HR only to the transition from DM1 to DM2 (TP6) is not entirely appropriate. However, the ERG considers it more reasonable to apply some adjustment than to retain the company's assumption that outcomes for chemotherapy and erlotinib/gefitinib are equivalent. The inclusion of this HR has only a minor impact on the ICER for osimertinib versus active monitoring (company's base case ICER = £12,849 per QALY gained; ICER including HR applied to TP6 = £12,649 per QALY gained).

In response to a request for clarification from the ERG[16] (question B7), the company amended their base case model to include the application of this HR for patients receiving PDC (see Section 5.3.5).

(7) Effectiveness of re-treatment with osimertinib

The company's model assumes that patients in the adjuvant osimertinib group who develop distant metastases and are re-treated with osimertinib will have the same event risks as those who have not previously been treated with osimertinib (each based on data from FLAURA[63]). As acknowledged in the CS[1] (page 28), this is subject to uncertainty and no evidence exists to support this assumption. The ERG's clinical advisors commented that they would expect osimertinib to be clinically effective in the re-treatment setting, but that they would expect effectiveness to be lower than that for a population of patients who have not previously received osimertinib.

In response to a request for clarification from the ERG[16] (question B8), the company provided further justification for the assumption of equivalent outcomes irrespective of prior osimertinib use. The company's response states: *"Clinicians unanimously agreed that should a patient successfully complete 3 years of treatment with osimertinib in the adjuvant setting but subsequently relapse after a DF period of at least 6 months then there is no clear clinical rationale as to why the effectiveness of osimertinib should differ when used in the metastatic setting. Clinicians advised that if a patient has completed 3 years of treatment with osimertinib in the adjuvant setting, then it was likely that patients had not developed TKI-resistant mechanisms, and as a result, further treatment with osimertinib with in the 1L mNSCLC disease setting was unlikely to result in a reduced efficacy profile."*

However, as noted in critical appraisal point [2], personal communication from NHSE indicated that if osimertinib was recommended in the adjuvant setting, TKIs would not be available as downstream treatments. The company's sensitivity analyses indicate that the inclusion of re-treatment has little impact on the ICER for adjuvant osimertinib, as re-treatment is assumed only after 5 years, which coincides with the timepoint at which the company's cure assumption is applied, and only 50% of these patients are assumed to be re-treated.

(8) Uncertainty regarding representativeness of FLAURA to the target population following distant relapse

The ERG notes that the patient population enrolled into the FLAURA trial[63] were required to have a WHO PS of 0 or 1 at baseline, and therefore may not fully reflect those patients in the target population who subsequently experience distant relapse. The company's clarification response[16] (question B6) notes that: patients who relapse following complete surgical resection for early-stage NSCLC are distinct from patients with untreated, locally-advanced or metastatic NSCLC; patients under active surveillance are likely to be diagnosed with relapse more quickly than patients who present with distant metastases; the recommendation for osimertinib in the metastatic setting is not restricted by PS (even though FLAURA was); patients with EGFRm-positive disease tend to be younger and fitter, and whilst the data from ADAURA[37] are immature, more than [redacted] of patients in each group had a PS of 0 or 1 at relapse. The ERG believes that the company's clarification response further supports the use of data from FLAURA to reflect downstream outcomes for patients with distant metastases, but notes that there remains some uncertainty regarding whether the trial data are representative of the patient population that the DM1 state of the model is intended to reflect. Nonetheless, the ERG is satisfied that this is the most appropriate source to inform these transitions in the model.

(9) Assumption of indefinite relative treatment effects for osimertinib in the metastatic setting

The company's model applies separate Weibull survival models for TP6 (DM1 to DM2) for patients receiving osimertinib or PDC for metastatic disease. Similarly, separate models are applied for TP8

(DM2 to dead). The model implicitly assumes a lifetime relative treatment effect for osimertinib. In NICE TA654,[29] the NICE Appraisal Committee concluded that the assumption of a lifetime treatment effect for osimertinib was optimistic and that the ERG's preferred scenarios, which assumed a treatment effect duration of 3-5 years, were more appropriate. This represents an inconsistency between the adjuvant osimertinib model and the model used to inform TA654.

(10) Issues relating to utility values applied in the company's model

The ERG has three main issues relating to the utility values applied in the company's model; these can be summarised as follows:

(i) The utility value applied in the DF and LRR health states is higher than that for the age- and sex-matched population and is thus implausible

(ii) The utility value applied in the DM1 state may be implausibly high

(iii) The model does not include HRQoL decrements for potential late effects of adjuvant treatment or AEs associated with downstream treatments.

(i) Implausible utility value applied in the DF and LRR health state

The company's model applies a utility value of [redacted] in both the DF and LRR health states, based on an RMME model fitted to SF-36 data from ADAURA[37] mapped to the EQ-5D-3L. Whilst the model includes the adjustment of utilities for increasing age, the model assumes that HRQoL for people with NSCLC who are free from distant metastases is consistently better than that for the general population (see Figure 19, red line [DF and LRR utility] versus dashed black line [general population utility]). The ERG and their clinical advisors do not consider this to be plausible. The CS[1] acknowledges that this finding is counterintuitive, but provides some justification through reference to a published utility value of 0.84 for people with NSCLC with stable disease.[97] However, the ERG also considers that this published estimate is implausible, as again, it implies that people with NSCLC have a better level of HRQoL than the general population. The ERG's clinical advisors further commented that it was not reasonable to assume that patients who have loco-regional recurrence have the same level of HRQoL as those who are disease-free, due to the cumulative impact of treatments received (surgery, radiotherapy and/or chemotherapy). The use of implausible utility values in the DF state will favour the adjuvant osimertinib group, whilst applying the same value in the LRR state will favour the active monitoring group.

Figure 19: Comparison of the health state utility values applied in the company's model (both groups) and age- and sex-matched utility estimates from Ara and Brazier

The ERG also notes that the utility value applied in these health states have been derived using linear RMME models. These models make the assumption of normality of model residuals, yet EQ-5D-3L data are known to be non-normally distributed (as demonstrated by the point estimates and 95% CIs in CS[1] Table 30). The ERG considers that a mixture model (for example, an adjusted limited dependent variable mixture model[98]), rather than a linear RMME model, may have been better able to reflect the underlying distribution of the EQ-5D data. The company's clarification response[16] (question B17) presents the residuals from the RMME model and indicates that whilst these are not perfectly normally distributed, the differences did not appear to be significant. The ERG notes that this RMME model is not used in the company's updated base case model (see Section 5.3.5).

(ii) Implausible utility value applied in the DM1 health state

The company's model applies a utility value of 0.794 to patients in the DM1 health state. This utility value was taken from NICE TA654[29] and was derived by mapping the available EORTC QLQ-C30 data in FLAURA[63] to the EQ-5D-3L. The ERG notes that the utility value obtained from this mapping exercise is very similar to the utility for the age- and sex-matched general population (see Figure 19, blue line [DM1 utility] versus dashed black line [general population utility]). The ERG's clinical advisors commented that the utility value applied in this health state appears to be implausibly high and that it is unlikely to reflect the cumulative negative impacts of treatment. The ERG's clinical advisors

did however agree that it is plausible that HRQoL would be lower for patients with progressed disease compared with those who are receiving first-line treatment for metastases (see Figure 19, green line [DM2 utility] versus blue line [DM1 utility]). The ERG notes that neither FLAURA[63] nor Labbé *et al*.[72] were included in the company's SLR of HRQoL studies (CS Appendix H,[36] Table 18), although both studies were used in the model used to inform NICE TA654.[29]

(iii) Absence of negative HRQoL impacts of late effects of adjuvant treatment and AEs associated downstream treatments

The company's model does not include any long-term impacts on HRQoL of late effects of adjuvant treatments and surgery, for example, chronic fatigue, immunosuppression, recurrent infections and cardiac and pulmonary toxicity following curative treatment. This exclusion may advantage adjuvant osimertinib, although the ERG believes that limited data exist through which to quantify such effects.

In addition, the model does not explicitly include any HRQoL losses associated with AEs resulting from downstream treatments for loco-regional or distant metastases. The ERG believes that the inclusion of these negative health impacts would increase the incremental QALY gain and lower the ICER for adjuvant osimertinib due to the higher proportion of relapsed patients in the active monitoring group.

Summary of utility values applied in previous models of treatments for EGFRm-positive NSCLC

Table 44 summarises the health state utility values applied in models used to inform previous NICE TAs of treatments for EGFRm-positive metastatic NSCLC. Where information is available, it is clear that most appraisals have applied utility values in the PF health state which are high compared with, or higher than, general population values. The table also indicates that with the exception of TA258,[99] the utility values applied in the progressed disease (PD) state are broadly similar to those used in the DM2 state of the adjuvant osimertinib model. As all previous NICE TAs in EGFRm-positive NSCLC relate to the metastatic setting, no alternative utility values are available for comparison with the DF and LRR health states. The company's SLR of HRQoL studies identified only one potentially useful additional source (Andreas *et al*.[14]) which is already included in the company's scenario analyses (see Table 39, Analysis S13). The use of these alternative values had only a minor impact on the ICER.

Table 44: Summary of health state utility values applied in previous NICE TAs of treatments for EGFRm-positive NSCLC (locally advanced or metastatic)

NICE TA	Health states and utility values	Source and valuation method
TA654[29]	PF = 0.794 PD = 0.678	FLAURA[63] (EORTC QLQ C30 mapped to EQ-5D-3L, trial patients)
TA653[34]	*Model (a)* PFS = 0.831 SD = 0.751 PD = 0.715	Based on utility values used in TA416[100] (valuation method unclear*)
	Model (b) PF = 0.836 SD = 0.797 PD = 0.717	AURA3[89] (EQ-5D-5L mapped to EQ-5D-3L, trial patients)
TA595[33]	PF (treatment-specific) = redacted PD = 0.64	PF utilities from ARCHER 1050 trial[101] (EQ-5D-3L, trial patients) PD utility value from Labbé *et al*[72] (EQ-5D-3L, NSCLC patients)
TA310[32]	1L PF = 0.784	LUX-Lung[102] (EQ-5D-3L, trial patients)
	2L PF = 0.73	Chouaid *et al.*[103] (EQ-5D-3L, NSCLC patients)
	3L BSC = 0.46	
	3L PF = 0.62	
TA258[99]	Erlotinib PFS = 0.661 Gefitinib PFS = 0.656 PD disutility = -0.18	Calculated using various utility estimates reported by Nafees *et al*.[73] (standard gamble, general population)

TA - Technology Appraisal; PF - progression-free; PD - progressed disease; SD - stable disease; BSC - best supportive care; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer quality of life questionnaire; EQ-5D-3L - Euroqol 5-Dimensions (3-level); EQ-5D-5L - Euroqol 5-Dimensions (5-level); NSCLC - non-small-cell lung cancer; L - line

In response to a request for clarification from the ERG (see clarification response,[16] question B20) the company acknowledged the limitations of their mapping analyses and updated the utility value for the DF and LRR states to reflect the estimated mean utility for the age- and sex-matched general population (utility = 0.81).[71] This forms part of the company's updated base case (see Section 5.3.5).

(11) Issues relating to costs

The ERG has a number of issues relating to the costs applied in the company's model. These can be summarised as follows:

(i) Inappropriate assumptions regarding monitoring costs of treatments

(ii) No AE costs are included for treatments related to downstream treatments for recurrence

(iii) Inappropriate assumptions regarding EGFRm testing costs

(iv) The resource use values applied for CNS metastases radiotherapy do not reflect UK clinical practice

(v) Excluded and inappropriate treatment costs

(vi) Exclusion of costs associated with drug wastage.

(i) Inappropriate assumptions regarding monitoring costs of treatments

The company's model includes the cost of treatment monitoring for PDC (liver and renal function tests and full blood counts) and for docetaxel (full blood counts only); these costs are applied in each cycle in which treatment is given. No monitoring costs are assumed for osimertinib in either the adjuvant or metastatic settings. The ERG's clinical advisors commented that the monitoring costs for osimertinib and docetaxel would be the same as those used for PDC. As such, the ERG believes that the company's model underestimates the costs of treatment monitoring for both osimertinib and docetaxel. In addition, the ERG's clinical advisors commented that patients receiving osimertinib would require monthly ECGs for the first few months of treatment, switching to alternate months once the patient is established on treatment. These issues impact on both treatment groups. The company's clarification response[16] (question B22) addresses this issue; the company's updated model includes monitoring costs for osimertinib based on FLAURA[63] and ADAURA.[37] Further details of these updated costs are described in Table 13 of the company's clarification response.

(ii) Exclusion of adverse event costs for downstream treatments

The costs of managing AEs are applied only for those events which occur in the DF health state, based on the event frequencies observed in ADAURA.[37] The company's model does not explicitly include costs associated with managing AEs resulting from downstream treatments for loco-regional or distant metastases. The company's clarification response[16] (question B27) highlights that given the treatment pathways assumed in the model and the expectation that fewer people receiving adjuvant osimertinib will experience loco-regional and distant relapse, the inclusion of costs associated with AEs from downstream treatments would be higher for the comparator group, thereby resulting in a lower ICER for adjuvant osimertinib. The ERG agrees with the company's view.

The ERG also notes that some of the AE costs included in the model appear to be implausibly high (e.g. £1,509.22 for treating paronychia). However, given the low frequency of AEs in each treatment group, the net impact on the ICER is minimal.

(iii) Inappropriate assumptions regarding EGFRm testing costs

The company's model applies the cost of a single EGFR test per patient treated with osimertinib. This cost is applied to all patients in the DF state in the adjuvant osimertinib group, and to all patients who reach DM1 in the active monitoring group. However, the EGFR positivity rate in patients with NSCLC is approximately 10-15%, which means that for every one EGFRm-positive patient who is eligible for treatment with osimertinib, around 6 to 9 patients would return a negative EGFR test result. As such, the costs of EGFRm testing are underestimated, as the costs of testing patients who return a negative result are not included. The ERG's clinical advisors also commented that if patients were to be re-treated with osimertinib in the metastatic setting then they would need to be re-tested; these costs are

not included in the company's model (although personal communication from NHSE suggests that re-treatment and hence re-testing costs are not appropriate). The ERG believes a more appropriate approach would involve multiplying the test cost by one divided by the EGFRm positivity rate.

The company's updated base case model which was provided following the clarification round includes this higher cost. The company's clarification response[16] (question B26) notes however that this is likely to be an overestimate as a proportion of patients are already routinely tested for EGFR mutations in NHS practice and that many patients undergo REFLEX testing for a range of biomarkers as part of a next generation sequencing panel, including EGFR, anaplastic lymphoma kinase (ALK) mutations and programmed death-ligand 1 (PD-L1) status. As such, the company considers their updated base case to be conservative. The ERG's clinical advisors agreed that some patients may already be tested, but commented that these patient are not typically those with early-stage operable lung cancer.

(iv) Inappropriate resource use values applied for CNS metastases radiotherapy

The model applies radiotherapy costs associated with CNS metastases as a once-only cost for people entering the DM1 health state, for a specified proportion of patients. The model assumes that 50% of these patients will receive six doses of stereotactic radiotherapy, with the remaining 50% receiving one dose of whole brain radiotherapy. The ERG's clinical advisors commented that they would expect patients receiving stereotactic radiotherapy to receive only one dose (rather than six) and that patients receiving whole brain radiotherapy would receive at least two doses (rather than one). In TA536[78], it was highlighted that clinical practice was moving away from whole brain radiotherapy for CNS metastases towards using steroids instead. The ERG's clinical advisors agreed with this point and noted that it is more likely that around 66% of patients receive stereotactic radiotherapy and 34% receive whole brain radiotherapy.

The company's clarification response[16] (question B25) comments that the number of fractions of stereotactic radiotherapy and whole brain radiotherapy were accepted in TA536.[78] These assumptions have not been amended within the company's updated base case model; however, the company presented a scenario analysis to assess the impact of applying the ERG's advisors' preferred assumptions on the number of fractions (see Section 5.3.5, Table 46).

(v) Excluded and inappropriate treatment costs

As discussed in critical appraisal point [2], the company's modelled pathway does not fully reflect the description of the treatment pathway in CS[1] Figure 3. The exclusion of single-modality radiotherapy and surgery for loco-regional recurrence and the ABCP regimen and other TKIs for distant metastases in the modelled pathway impacts on both health outcomes and costs. The ERG's clinical advisors also commented that if radiotherapy were to be used in the LRR health state, despite not being included in

Figures 3 and 4 of the CS[1], external beam radiotherapy would be given as opposed to single fraction brachytherapy used in the model. In addition, the ERG's clinical advisors noted that drug administration costs, shown in CS Table 43, exclude the use of supporting medications such as anti-emetics and granulocyte colony stimulating factor (G-CSF).

The company's clarification response[16] (question B29) comments the need for anti-emetics in practice is low, only [redacted] of patients in ADUARA experienced nausea, and these treatments are inexpensive; hence, the impact of excluding these costs from the model is expected to be minor. In addition, the company's updated model assumes that external beam radiotherapy (rather than brachytherapy) is used for loco-regional recurrence and that 18% of patients receive single-modality radiotherapy (rather than chemoradiation). Additional scenarios are also presented to explore the impact of alternative downstream treatment pathways in the active monitoring and adjuvant osimertinib groups (see Section 5.3.5, Table 46).

(vi) Exclusion of costs associated with drug wastage

The company's model does not include the costs associated with drug wastage. The model assumes vial sharing is permitted for IV chemotherapy drugs (pemetrexed, cisplatin and docetaxel) and that oral treatment with osimertinib does not incur any wastage. However, vial sharing may not be permitted and patients may not complete a prescribed course of osimertinib, for example due to death part-way through a cycle. Excluding wastage in the model will underestimate costs in both treatment groups.

The company's updated base case model includes wastage costs for PDC and docetaxel (see clarification response,[16] question B28 and Section 5.3.5, Table 45). However, the updated model does not include any wastage costs for osimertinib.

Overall, the ERG believes that the company's updated model and scenario analyses address the majority of the ERG's concerns regarding costs.

(12) Comparison of observed and predicted DFS and OS

Figure 20 and Figure 21 present comparisons of observed DFS and OS in ADAURA[37] compared against the predictions from the company's model. Figure 22 presents a comparison of observed OS in FLAURA[63] against model-predicted OS for patients starting in DM1 (note – this plot was provided in the company's response to clarification question C2[16] and includes several model corrections).

Figure 20: Observed and model-predicted DFS, based on ADAURA and company's model (re-drawn by the ERG using the company's updated model)

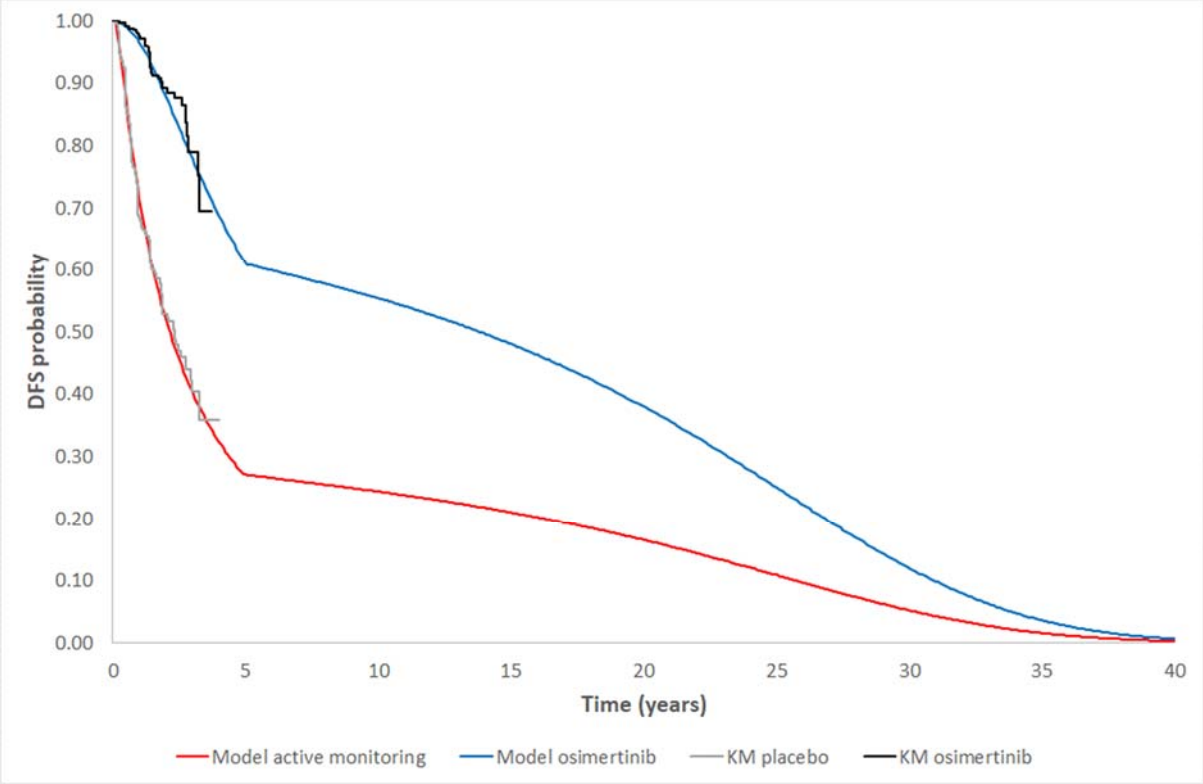


Figure 21: Observed and model-predicted OS, based on ADAURA and company's model (re-drawn by the ERG using the company's updated model)

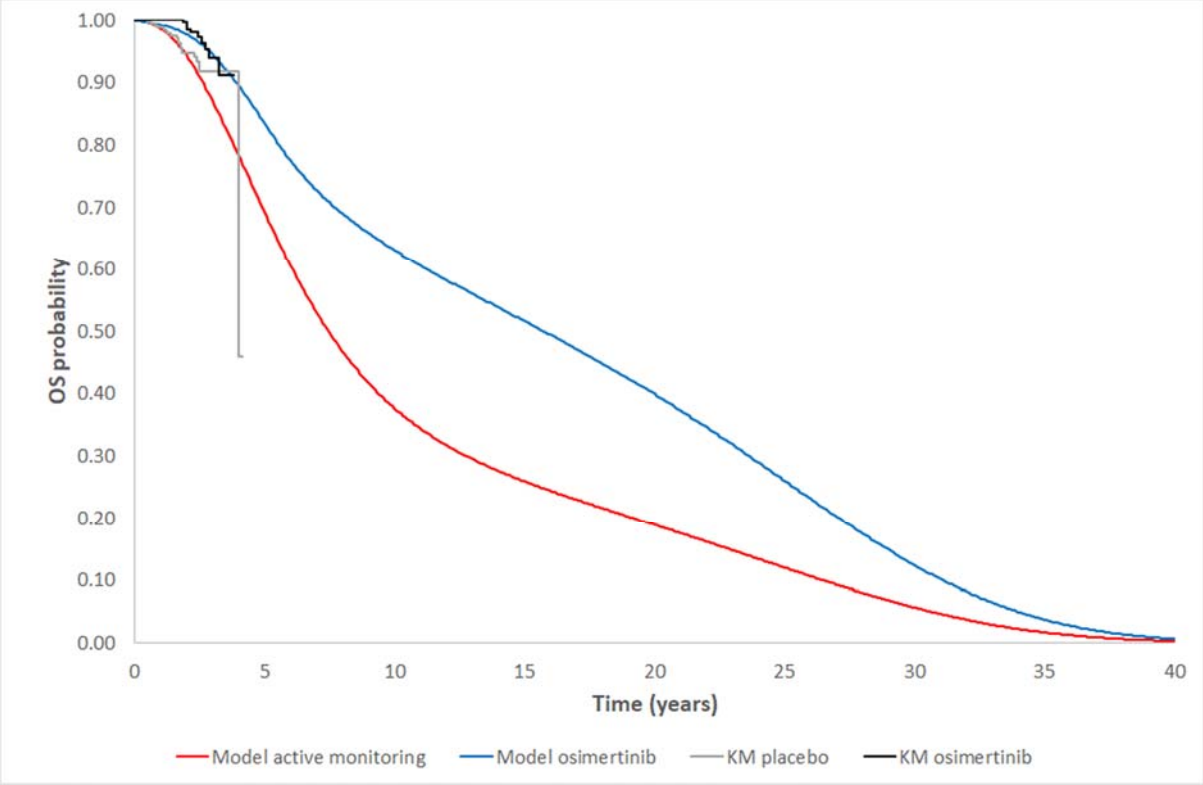


Figure 22: Observed and model-predicted OS for patients with distant metastases, FLAURA and company's model (reproduced from company's clarification response, question C2)

The ERG notes the following observations regarding the company's modelled predictions of DFS (Figure 20):

- Within the observed period of ADAURA,[37] the model appears to provide a good representation of DFS in both treatment groups.
- The company's model predictions of DFS (Figure 20) suggest a sharp "kink" in the cumulative probability of remaining disease-free at 5-years. This is a consequence of the company's cure assumption, whereby the predicted probabilities obtained from the parametric survival models for DM1 and DM2 are reduced by 95% from 5 years. The ERG considers it unlikely that longer follow-up in ADAURA[37] would indicate such a sharp change in the empirical hazard function for DFS.

The ERG notes the following observations regarding the company's modelled predictions of OS (Figure 21):

- The observed Kaplan-Meier plots of OS of osimertinib and placebo appear to converge at approximately 3.5 years. The ERG notes that whilst the available OS data are very immature, any estimate of incremental OS obtained from the company's model should be considered highly uncertain.
- Figure 21 suggests that the company's model may be under-estimating survival in the active monitoring (placebo) group after around 2 years. The precise reasons for this are unclear, however, the ERG believes that this may be a consequence of the misspecification of one or more of the parametric survival models used to estimate transition probabilities; or differences

between the populations included in the ADAURA,[37] FLAURA[63] and CancerLinQ datasets.[64] The ERG tested a number of alternative combinations of parametric survival models but was unable to obtain a better fit to the observed data. The company's clarification response[16] (question B30) also notes that the model predictions are consistent with the OS data from ADAURA[37] up to 24 months, and highlights the immaturity of the trial data. The company's response further comments that the overall model predictions were consistent with the expectations of the company's clinical experts and with the 8-year OS data for the placebo arm of the ANITA trial.[85]

- The ERG's clinical advisors considered the company's modelled OS function for the active monitoring group to be clinically plausible (Figure 21, blue line). However, they noted the caveat that clinicians tend to consider survival probabilities out to 5 years, rather than 40-years.
- As discussed in critical appraisal point [4], the ERG's clinical advisors considered the company's modelled OS function for the adjuvant osimertinib group and the incremental OS benefit suggested by the model (Figure 21, red line versus blue line) to be highly uncertain, and noted that the modelled OS gain for adjuvant osimertinib may be optimistic. In particular, they noted that they would expect a smaller gap between the two groups as a consequence of osimertinib being available as a treatment for metastatic disease in the active monitoring group.

With respect to modelled OS for patients with distant metastases (see Figure 22), the ERG notes that the company's model provides a good fit to the observed data from FLAURA,[63] which provides some reassurance regarding the credibility of the downstream portion of the model.

(13) Absence of subgroup analyses in patients with stage 1B NSCLC

The final NICE scope[22] states that *"If the evidence allows, subgroups based on NSCLC stage (IB versus II-IIIA) may be considered."* The company's economic model reflects the overall population of ADAURA[37] and the CS[1] does not report an economic subgroup analysis for patients with stage 1B NSCLC. As part of the clarification process (question C3), the ERG requested that the company perform this subgroup analysis.[16] The company did not undertake this analysis, noting that the available data are limited for the stage 1B subgroup ([redacted] and [redacted] events for osimertinib and placebo, respectively) and that the study was not powered to assess the efficacy of osimertinib by stage of disease. The company did however present a subgroup analysis for patients with stage II-IIIA NSCLC, which resulted in an ICER of £5,292 per QALY gained.

The ERG agrees that the limited event numbers for patients with stage IB disease will inevitably lead to considerable uncertainty in the resulting estimates of cost-effectiveness for this subgroup. However, the ERG also believes that this is a potentially important area of heterogeneity and that the lower ICER

reported for the stage II-IIIA NSCLC subgroup indicates that the ICER will be higher in the stage IB population than in the overall population.

5.3.5 Company's updated model provided following the clarification round

As discussed throughout Section 5.3.4, the company submitted an updated base case model as part of their clarification response.[16] The company's updated base case model includes the following amendments (see company's clarification response, Appendix A):

- Correction of all errors listed in Table 42, except for items 5, and 17 and 19.
- Radiotherapy received in the LRR health state was changed from brachytherapy to external beam radiotherapy
- A proportion of patients (18%, informed by clinical opinion) in the LRR state were assumed to receive single-modality radiotherapy, with the remainder receiving chemoradiation
- The cost of EGFRm testing was updated to account for the number needed to test
- The cost of vial wastage was included for chemotherapy regimens
- The utility values for the DF and LRR states were set equal to that of the general population (utility = 0.810 [prior to age adjustment])
- The efficacy of chemotherapy-treated patients in the DM1 health state was adjusted using an HR of 0.43 (from Holleman *et al*.[91])

It should be noted that some further minor errors were identified by the ERG and these have not been addressed in the company's updated model. The company's updated base case results are shown in Table 45; the correction of the errors identified by the ERG, together with the additional model amendments result in a lower probabilistic ICER of £11,314 per QALY gained. The updated deterministic ICER is very similar to the probabilistic estimate.

Table 45: 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]	**£11,314**
Active monitoring	[redacted]†	[redacted]	[redacted]	-	-	-	-
Deterministic model							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,136**
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 ERG by modifying the company's VBA sub-routine for performing PSA

An updated cost-effectiveness plane and CEACs can be found in Appendix A of the company's clarification response.[16] These do not suggest a different conclusion to the original model; these are not reproduced here.

The company's clarification response also includes additional scenario analyses using the updated base case model. These include:

- Assuming that 10% of patients in DM1 and 25% of patients in DM2 do not receive active treatment (this affects costs but not outcomes)
- Including the ABCP regimen in DM2 for 16% of patients who have previously received a TKI, based on data on time to treatment discontinuation and time to death from the IMPower150 trial[18]
- Including earlier TKIs (afatinib, erlotinib, gefitinib and dacomitinib) for [redacted] of patients in DM1 in the active monitoring group. This analysis applies relevant treatment costs for each TKI and uses event risks based on the erlotinib/gefitinib arm of FLAURA.[63]
- Alternative cure assumptions (different cure timepoints and different subsequent risk reductions)
- Alternative number of doses of radiotherapy for CNS metastases
- Separate results for men and women.

The results of these additional scenario analyses are summarised in Table 46. These additional scenario analyses indicate that the ICER for adjuvant osimertinib is sensitive to the assumptions regarding first-line treatments for distant metastases and to assumptions regarding cure.

Table 46: Summary of company's additional scenario analyses following clarification

Scenario analysis description	Inc. QALYs	Inc. costs	ICER
Updated base case	[redacted]	[redacted]	**£11,136**
Assume some patients do not receive active treatment	[redacted]	[redacted]	**£12,932**
Inclusion of second-line ABCP	[redacted]	[redacted]	**£10,298**
Inclusion of early TKIs in active monitoring DM1	[redacted]	[redacted]	**£19,090**
Osimertinib cure at 6 years, 95% max cure rate. Placebo cure rate at 5 years, max cure rate: 95%.	[redacted]	[redacted]	**£14,958**
Osimertinib and placebo cure at 5 years, max cure rate: 85%	[redacted]	[redacted]	**£11,703**
Osimertinib cure at 6 years, max cure rate: 85%. Placebo cure rate at 5 years, max cure rate: 85%.	[redacted]	[redacted]	**£15,123**
Osimertinib linear increase from year 5 to 10, max cure rate: 95%. Placebo cure rate at 5 years, max cure rate: 95%.	[redacted]	[redacted]	**£18,822**
Amendment to number of doses of radiotherapy for CNS metastases	[redacted]	[redacted]	**£11,361**
Patient population: 100% female	[redacted]	[redacted]	**£10,675**
Patient population: 100% male	[redacted]	[redacted]	**£12,280**

QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ABCP - atezolizumab, bevacizumab, carboplatin and paclitaxel; TKI - tyrosine kinase inhibitor; DM1 - first-line treatment for distant metastases; CNS - central nervous system

5.4 Exploratory analyses undertaken by the ERG

5.4.1 ERG exploratory analysis – methods

The ERG undertook exploratory analyses using the company's updated base case model.[16] The ERG's preferred analyses include: correcting three minor errors contained in the company's updated model; removing the possibility of re-treatment; capping the treatment effect of osimertinib in DM1 at 5 years; applying alternative administration costs for chemotherapy and amending the acquisition cost for docetaxel; including costs of wastage for osimertinib, and including ABCP as a second-line treatment option for patients with distant metastases who have previously received a TKI. The ERG's preferred analyses include all of these amendments. Owing to the uncertainty surrounding the probability and timing of cure following adjuvant osimertinib and its impact on survival, the ERG's preferred exploratory 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 cure timepoint for the adjuvant osimertinib group is applied after 8 years (i.e. 5 years plus the 3-year maximum osimertinib treatment time). The latter scenario was undertaken to reflect a potential situation whereby osimertinib delays some relapses rather than preventing them altogether. Results for the ERG's preferred analyses are presented using both the probabilistic and deterministic versions of the model.

Additional sensitivity analyses were undertaken using both the ERG's preferred optimistic and pessimistic models. These included: using alternative utility values from Andreas *et al.*;[14] assuming that AEs associated with adjuvant osimertinib persist for 1 year (rather than 1 month); including a mix of TKIs as first-line treatments for patients in the active monitoring group; applying alternative parametric survival models to represent TP1 (DF to LRR) and TP2 (DF to DM1); halving the costs of EGFRm testing; including re-treatment with osimertinib for patients with distant metastases, and applying alternative assumptions regarding the number of patients receiving whole brain radiotherapy for CNS metastases. A final analysis was conducted to explore the impact of assuming a range of alternative cure timepoints in the adjuvant osimertinib group.

All analyses were implemented by two modellers to ensure that they are free from errors. Where possible, analyses were implemented using existing menus which were already programmed into the company's updated model.

It should be noted that confidential comparator PAS (cPAS) discounts are available for bevacizumab, atezolizumab, afatinib, gefitinib and dacomitinib. These drugs are included in some of the ERG's exploratory analyses. The results of the ERG's exploratory analyses including these discounts are provided in a separate confidential appendix to this report.

ERG Exploratory Analysis 1: Correction of model errors

The company's updated model includes the correction of most of the errors listed in Table 42. The company did not apply a weighted survival model for general population mortality (Item 5), used incorrect proportions for the number of CNS recurrences in DM1 (Item 17), and erroneously assumed that disutilities associated with AEs persist over 1 year rather than 1 month (Item 19). These three minor issues are corrected in this ERG's exploratory analysis. All subsequent ERG exploratory analyses include the correction of these errors.

ERG Exploratory Analysis 2: Re-treatment not permitted

NHSE has indicated that if osimertinib is recommended in the adjuvant setting, the NHS would not allow further TKIs to be used for relapsed disease. Within this analysis, re-treatment with osimertinib is assumed to not be permitted.

ERG Exploratory Analysis 3: Treatment effects for osimertinib in DM1 capped at 5 years

For consistency with the final appraisal determination (FAD) for TA654,[29] 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.

ERG Exploratory Analysis 4: Alternative cost assumptions

Within this analysis, the costs of chemotherapy administration were set equal to the costs of day case attendances; this amendment was based on clinical advice received by the ERG. In addition, the cost of docetaxel was based on the value reported in eMIT[75] rather than the higher price listed in the BNF.[74]

ERG Exploratory Analysis 5: Inclusion of osimertinib wastage

Within this analysis, patients who die before reaching the 3-year maximum treatment duration on adjuvant osimertinib, and patients who receive first-line osimertinib for distant metastases and leave the DM1 state, are assumed to incur wastage costs. The ERG analysis assumes that these patients will, on average, waste half a pack of osimertinib.

ERG Exploratory Analysis 6: Inclusion of ABCP as a second-line treatment

Within this analysis, ABCP is assumed to be a treatment option for patients reaching the DM2 health state. In line with the company's clarification response[16] (question A4), the analysis assumes that 16% of patients receive ABCP, with outcomes modelled according to TTD and OS from the IMPower150 trial.[18] It should be noted that this is only included as a second-line option if a TKI is used beforehand; hence, it is not included in the adjuvant osimertinib pathway if re-treatment is not permitted (the no re-treatment pathway is instead PDC followed by docetaxel).

ERG Exploratory Analysis 7: Assumption of 8-year cure timepoint for adjuvant osimertinib (applied to transitions out of the DF state - TP1 and TP2)

Within this analysis, the timepoint for cure in the adjuvant osimertinib group was moved to 8 years to reflect a scenario is which some recurrences are delayed, rather than prevented.

ERG Exploratory Analysis 8: ERG-preferred analysis

The ERG's preferred optimistic scenario combines ERG Exploratory Analyses 1-6. The ERG's preferred pessimistic scenario combines ERG Exploratory Analyses 1-7 (i.e. including the 8-year cure timepoint for the adjuvant osimertinib group).

Nine sets of additional sensitivity analyses were conducted using the ERG's optimistic and pessimistic analyses.

ERG Additional Sensitivity Analysis 1: Use of utility values from Andreas *et al.*[14]

Within this analysis, alternative utility values reported by Andreas *et al.*[14] were included in the company's model (health state utilities: DF=0.72; LRR=0.62; DM1 and DM2=0.59). This analysis is equivalent to a scenario analysis presented in the CS[1] (see Table 39, Analysis SA14).

ERG Additional Sensitivity Analysis 2: Adjuvant osimertinib QALY loss extended to 1-year

Within this analysis, the disutilities associated with AEs for patients receiving adjuvant osimertinib were assumed to persist for 1-year rather than 1 month.

ERG Additional Sensitivity Analysis 3: Inclusion of mix of TKIs in DM1 in active monitoring group

Within this analysis, a mix of TKIs is assumed to be used in the first-line position for patients who develop distant metastases following active monitoring. This analysis is equivalent to the early TKIs scenario presented in Table 3 of the company's fact check response, which is based on recent national prescribing data from Q1 2021.[5] The analysis assumes that [redacted] of patients in DM1 receive osimertinib whilst the remainder receive other TKIs; in addition, [redacted] of patients in DM2 also receive osimertinib, with the remainder receiving PDC. This is a pessimistic scenario given that osimertinib is more effective than older TKIs[91] and because osimertinib has received a positive NICE recommendation in the first-line setting. The ERG's clinical advisors believe that if adjuvant osimertinib were not to be recommended by NICE, the use of osimertinib as a first-line treatment for metastatic disease would further increase.

ERG Additional Sensitivity Analysis 4: Use of log-normal model for TP2 (DF to DM1)

Two additional analyses were conducted exploring the use of the log-normal model for TP2. This model was applied: (a) in both treatment groups and (b) in the adjuvant osimertinib group only.

ERG Additional Sensitivity Analysis 5: Use of log-logistic model for TP1 (DF to LR) and log-normal model for TP2 (DF to DM1), adjuvant osimertinib group only

This analysis extends the ERG's preferred pessimistic scenario, whereby the treatment advantage of adjuvant osimertinib reflects a delay of recurrence rather than an avoidance of recurrence. This analysis is presented using the ERG pessimistic scenario cure timepoints (5 years for active monitoring and 8 years for osimertinib), but with the additional assumption that the cumulative hazards (and hence survival) at these respective cure times will be approximately equal between the arms. The company's preferred survival models for TP1 and TP2 were retained for the placebo group and alternative survival models for these transitions were selected for the adjuvant osimertinib group. The ERG then selected models which had comparable (TP1) or better (TP2) statistical fit to the observed data than the company's preferred model and which replicated the 5-year placebo arm survival probability at approximately 8 years. For TP1, the placebo arm 5-year survival is 0.61 which is reached at 8.4 years with the log-logistic model for adjuvant osimertinib. For TP2, the placebo arm 5-year survival is 0.56 which is reached at 8.9 years with the log-normal model for adjuvant osimertinib. The ERG notes that this represents a highly pessimistic analysis.

ERG Additional Sensitivity Analysis 6: EGFRm test cost halved

Within this analysis, the cost of EGFRm testing was halved.

ERG Additional Sensitivity Analysis 7: Re-treatment with osimertinib included

Within this analysis, re-treatment with osimertinib is assumed to be permitted for patients who develop distant metastases.

ERG Additional Sensitivity Analysis 8: Alternative proportions receiving whole brain radiotherapy for CNS metastases

Within this analysis, 34% of patients with CNS metastases receive whole brain radiotherapy whilst the remaining 66% receive stereotactic radiotherapy.

ERG Additional Sensitivity Analysis 9: Alternative cure timepoints for adjuvant osimertinib group

This analysis presents the ICERs for the ERG preferred model assuming a range of cure timepoints for the adjuvant osimertinib group.

5.4.2 ERG exploratory analysis - results

ERG preferred analyses

Table 47 presents the results of the ERG's preferred analyses based on the deterministic version of the model. The correction of the remaining model errors reduced the ICER from £11,136 to £10,795 per

QALY gained; all subsequent ERG exploratory analyses are applied to this corrected model. Applying the treatment effect for osimertinib for 5 years in DM1 (EA3) increases the ICER to £11,815 per QALY gained. As shown in the table, assuming an 8-year cure point (EA7) has the greatest impact on the model results, increasing the ICER from £10,795 to £22,460 per QALY gained. The ERG's other model amendments only have a minor impact on the ICER. The ERG's preferred optimistic scenario (EA8), which combines ERG Exploratory Analysis 1-6, results in an ICER of £9,979 per QALY gained. The ERG's preferred pessimistic scenario (EA9), which additionally assumes an 8-year cure point for the adjuvant osimertinib group, results in an ICER of £20,417 per QALY gained. The results of the probabilistic model are slightly more favourable (ERG optimistic scenario: ICER = £9,838 per QALY gained; ERG pessimistic scenario: ICER = £20,301 per QALY gained; see Table 48).

Table 47: Results of the ERG's preferred analyses, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,136**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA1: Correction of remaining model errors							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,795**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA2: No re-treatment allowed for osimertinib							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,111**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA3: 5-year treatment effect for metastatic osimertinib DM1 to DM2							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,815**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA4: Update unit costs for administration of chemotherapy and docetaxel drug acquisition							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,742**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA5: Inclusion of wastage for osimertinib (0.50 packs)							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£10,657**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA6: Inclusion of ABCP treatment option							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£9,900**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA7: 8-year cure point applied							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,460**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA8: ERG preferred optimistic analysis (EA1-EA6 combined)							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£9,979**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA9: ERG preferred pessimistic analysis (EA1-EA7 combined)							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,417**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-

EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

** Undiscounted*

Table 48: Results of the ERG's preferred analyses, probabilistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA8: ERG preferred optimistic analysis (EA1-EA6 combined)							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£9,838**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-
EA9: ERG preferred pessimistic analysis (EA1-EA7 combined)							
Adjuvant osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,301**
Active monitoring	[redacted]	[redacted]	[redacted]	-	-	-	-

EA - exploratory analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

Results of additional sensitivity analyses undertaken using the ERG's preferred models

Table 49 shows the results of additional sensitivity analyses applied to the ERG's preferred optimistic and pessimistic models. As shown in the table, the inclusion of a different mix of TKIs for distant metastases in the active comparator arm (ASA3) has a substantial impact on the ICER for adjuvant osimertinib, with the ICERs increasing to £19,391 and £33,330 per QALY gained for the optimistic and pessimistic scenarios, respectively. The use of the log-normal model for TP2 (DF to DM1) in the osimertinib group only (ASA4b) increases the ICER from £9,979 to £13,224 per QALY gained in the optimistic scenario, and from £20,417 to £38,897 per QALY gained in the pessimistic scenario. The ERG's highly pessimistic scenario (ASA5) leads to a considerably higher ICER of £54,913 per QALY gained.

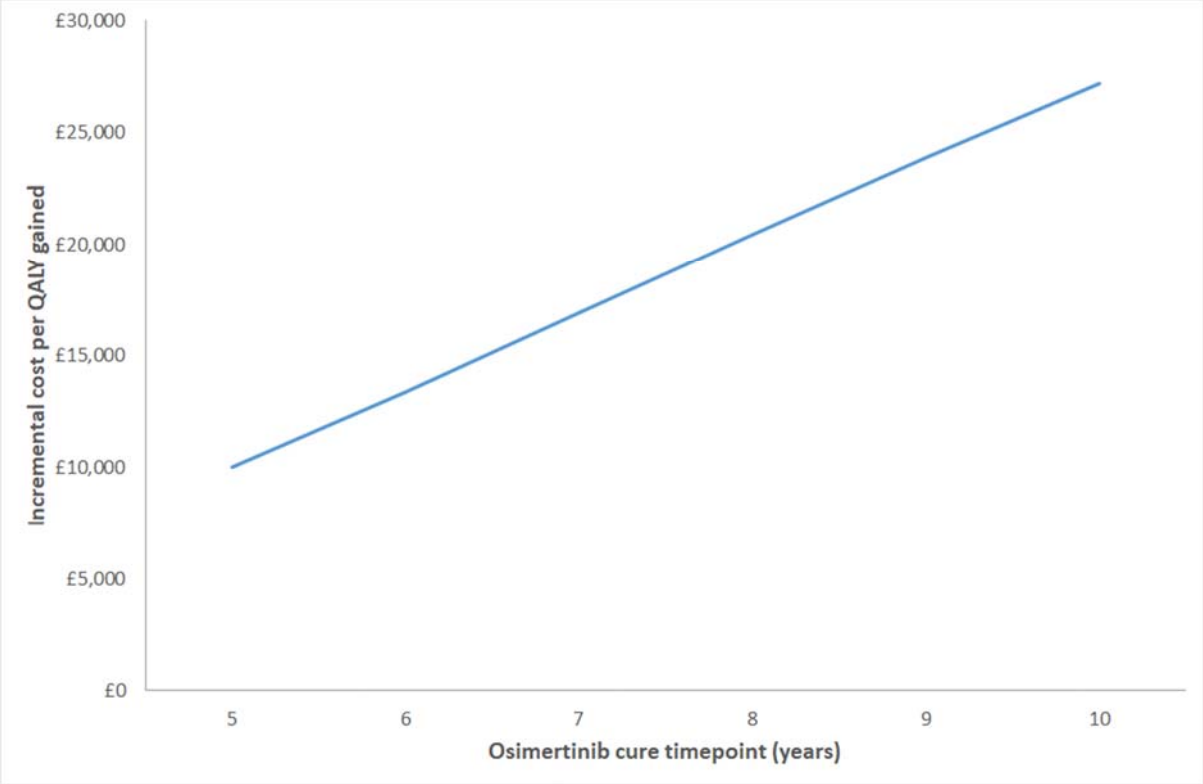
Table 49: Results of the ERG's additional sensitivity analyses

Additional sensitivity analysis	Optimistic scenario - cure point at 5 years for both groups				Pessimistic scenario - cure point at 8 years for osimertinib, 5 years for active monitoring			
	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis	[redacted]	[redacted]	[redacted]	**£9,979**	[redacted]	[redacted]	[redacted]	**£20,417**
ASA1: Use of utilities from Andreas	[redacted]	[redacted]	[redacted]	**£10,467**	[redacted]	[redacted]	[redacted]	**£21,032**
ASA2: Assume AE QALY loss for one year for adjuvant osimertinib	[redacted]	[redacted]	[redacted]	**£9,988**	[redacted]	[redacted]	[redacted]	**£20,442**
ASA3: Different mix of TKIs	[redacted]	[redacted]	[redacted]	**£19,391**	[redacted]	[redacted]	[redacted]	**£33,330**
ASA4a: Use log-normal for TP2 (DF to DM1) in both arms	[redacted]	[redacted]	[redacted]	**£9,334**	[redacted]	[redacted]	[redacted]	**£25,572**
ASA4b: Use log-normal for TP2 (DF to DM1) in treatment arm only	[redacted]	[redacted]	[redacted]	**£13,224**	[redacted]	[redacted]	[redacted]	**£38,897**
ASA5: Use log-logistic for TP1 (DF to LR) and log-normal for TP2 (DF to DM1), treatment arm only	Not applicable				[redacted]	[redacted]	[redacted]	**£54,913**
ASA6: Halve EGFR testing cost to account for some tests already	[redacted]	[redacted]	[redacted]	**£9,818**	[redacted]	[redacted]	[redacted]	**£20,185**
ASA7: Allow re-treatment with osimertinib	[redacted]	[redacted]	[redacted]	**£10,808**	[redacted]	[redacted]	[redacted]	**£22,989**
ASA8: Alternative proportion of patients receiving whole-brain radiotherapy for CNS metastases	[redacted]	[redacted]	[redacted]	**£9,857**	[redacted]	[redacted]	[redacted]	**£20,280**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental; ASA - additional sensitivity analysis; DF – disease-free; LRR - loco-regional recurrence; DM1 - first line distant metastasis; CNS - central nervous system; TKI - tyrosine kinase inhibitor; EGFR - epidermal growth factor receptor
**Undiscounted*

The ERG undertook additional sensitivity analyses using a wider range of timepoints for cure in the adjuvant osimertinib group, whilst holding this assumed cure timepoint fixed at 5 years in the active monitoring group (see Figure 23). Based on the ERG's preferred model, the ICER ranged from £9,979 per QALY gained with a 5-year cure point to £27,179 per QALY gained with a 10-year cure point.

Figure 23: Impact of adjuvant osimertinib cure point on the ICER



5.5 Discussion

The company's SLR[1] did not identify any existing economic analyses of adjuvant treatments in completely resected, stage IB–IIIA EGFRm-positive NSCLC (with or without adjuvant chemotherapy).

The CS[1] presents the methods and results of a *de novo* health economic model of osimertinib as adjuvant therapy versus active monitoring for patients with completely resected, stage IB-IIIA EGFRm-positive NSCLC. The model estimates the incremental cost-effectiveness of adjuvant osimertinib versus active monitoring over a lifetime horizon from the perspective of the NHS and PSS. The model adopts a state transition (semi-Markov) approach and includes five health states: (i) DF; (ii) LRR; (iii) DM1; (iv) DM2, and (v) dead. The model uses time-to-event data from ADAURA to estimate the time-dependent risk of loco-regional and distant recurrence for patients who are disease-free; other transitions, including those relating to mortality risk, are informed by external data (CancerLinQ,[64] FLAURA[63] and life tables[40]). Patients who remain disease-free are assumed to have no excess mortality risk. The model includes a key assumption whereby after 5 years, the predicted probabilities of relapse (either loco-regional or distant) applied in the DF health state are reduced by 95% in both treatment groups. This

increases the probability that patients remain disease-free and thus corresponds to a structural assumption of cure for most patients after this timepoint. The model also assumes that under current practice, all patients who develop distant metastases would receive osimertinib in the first-line setting (in DM1). Overall, the model predicts that adjuvant osimertinib: (a) increases DFS (as observed in ADAURA); (b) extends OS (as a consequence of improved DFS and the structural cure assumption); (c) increases adjuvant treatment costs (due to the costs of adjuvant osimertinib), and (d) reduces downstream treatment costs (largely as a consequence of fewer patients requiring osimertinib in the metastatic setting).

The probabilistic version of the company's updated model (post-clarification) suggests that the ICER for adjuvant osimertinib versus active monitoring is £11,314 per QALY gained. The deterministic ICER is similar (£11,136 per QALY gained).[16]

The ERG critically appraised the company's health economic analysis and double-programmed the deterministic version of the company's original model. The ERG's critical appraisal identified several issues relating to the company's original model and the evidence used to inform its parameters. These include: (i) the presence of several minor model errors; (ii) the exclusion of relevant downstream treatment options, in particular, the current use of TKIs and ABCP in the metastatic setting; (iii) uncertainty surrounding the company's cure assumption and predicted OS gains; (iv) the assumption that outcomes for patients receiving chemotherapy are equivalent to those for patients receiving TKIs; (v) concerns regarding the company's utility values applied in the DF and LRR health states; (vi) concerns relating to costs, including the assumption that only one EGFR test is required to identify a patient with an EGFR mutation, and (vii) the absence of subgroup analyses for patients with stage 1B NSCLC.

As part of the company's response to clarification questions from the ERG,[16] the company submitted an updated model which addresses several of the ERG's concerns. The company's updated base case model corrected the majority of errors identified by the ERG, amended costing assumptions and applied an HR to the TKI arm models to estimate outcomes for patients receiving chemotherapy in the model. Additional scenario analyses were presented which address some of the ERG's other concerns regarding the modelled treatment pathway.

The ERG undertook exploratory analyses using the company's updated model. These included: correcting three remaining model errors; removing the possibility of re-treatment with osimertinib; applying alternative administration costs for chemotherapy and amending the acquisition cost for docetaxel; including costs of wastage for osimertinib and including ABCP as a second-line treatment option for patients with distant metastases and assuming a later cure timepoint for adjuvant osimertinib.

The ERG presents two preferred analyses which reflect optimistic and pessimistic scenarios. The optimistic scenario includes all of the ERG's exploratory analysis and retains the company's original cure assumptions; the pessimistic analysis is identical, but additionally shifts the timepoint for cure to 8-years in the adjuvant osimertinib group. The ERG's preferred optimistic analysis suggests that the probabilistic ICER for adjuvant osimertinib versus active monitoring is £9,838 per QALY gained; the ERG's preferred pessimistic scenario suggests that the probabilistic ICER is £20,301 per QALY gained. The deterministic ICERs are similar. The ERG's exploratory analyses and additional sensitivity analyses indicate that the key driver of the ICER relates to the assumed cure timepoint(s) in the active monitoring and adjuvant osimertinib group. In addition, the ICER increases markedly when a mix of different (less expensive) TKIs is included as first-line treatment for distant metastases in the active monitoring group, and when alternative parametric survival models are applied to the probabilities of developing loco-regional and distant recurrence in the adjuvant osimertinib group.

6 END OF LIFE

NICE End of Life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The CS[1] does not make a case that adjuvant osimertinib meets NICE's End of Life criteria. The CS comments that median OS in the placebo arm of ADAURA was 48.2 months.[37]

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness conclusions

The clinical effectiveness evidence for adjuvant osimertinib is based on the ADAURA RCT of adjuvant osimertinib versus placebo (with or without adjuvant chemotherapy in both arms) for people with completely resected stage IB−IIIA EGFRm-positive NSCLC. Treatment duration in ADAURA was planned for 3 years or until disease recurrence or fulfilment of discontinuation criteria. However, the trial was unblinded two years early. Median duration of treatment was 22.5 months in the osimertinib arm and 18.7 months in the placebo arm.

There was a statistically significant DFS benefit for osimertinib: HR 0.20 (99.12% CI 0.14, 0.30; $p<0.001$). The statistically significant DFS benefit was observed across all pre-defined subgroups, including male/female sex, disease stages IB, II, and IIIA, and patients who had or had not received adjuvant chemotherapy. However, the magnitude of benefit was smaller for stage IB disease. In addition, distant and CNS recurrences accounted for a smaller proportion of the total recurrences in the osimertinib arm than in the placebo arm.

The main limitation of the ADAURA trial is that the OS data are immature, with only 9 deaths (2.7%) in the osimertinib arm and 20 deaths (5.8%) in the placebo arm; [redacted]. Therefore, it is uncertain whether the statistically significant DFS benefit will translate into a significant OS benefit. It is also uncertain whether the magnitude of DFS benefit will remain as large once longer follow-up has occurred.

AEs reported by ≥10% more patients with osimertinib than placebo included: diarrhoea; paronychia (infection of skin around nails); dry skin; pruritis (itch), and stomatitis (sore mouth). Decreased appetite, mouth ulceration and dermatitis acneiform were also numerically more common in the osimertinib arm than the placebo arm. In terms of AEs of special interest, ILD occurred in 3% in the osimertinib arm vs. 0% in the placebo arm (all mild or moderate in severity, one reported as serious), while cardiac AEs occurred in 5% (with 0.9% Grade ≥3 and one serious) in the osimertinib arm, and 3% (with 0.3% Grade ≥3 and none serious) in the placebo arm. Although adjuvant osimertinib is reasonably well-tolerated, low-grade AEs such as diarrhoea, paronychia and stomatitis may still be quite debilitating when the therapy is given over several years.

7.2 Cost-effectiveness conclusions

The probabilistic version of the company's updated model suggests that the ICER for adjuvant osimertinib versus active monitoring is £11,314 per QALY gained. The key uncertainties relate to the company's cure assumptions and their impact on expected survival gains.

The ERG's preferred analyses reflect two scenarios: (i) an optimistic scenario which retains the company's base case assumptions of cure at 5-years in both groups, and (ii) a pessimistic scenario in which the cure timepoint for the adjuvant osimertinib group is applied after 8 years (i.e. 5 years plus the 3-year maximum osimertinib treatment time). The latter scenario was undertaken to reflect a potential situation whereby osimertinib delays some relapses rather than preventing them altogether. Based on the probabilistic version of the ERG's preferred optimistic model, the ICER for adjuvant osimertinib is expected to be £9,838 per QALY gained. The ERG's preferred pessimistic scenario suggests a higher ICER of £20,301 per QALY gained. Additional sensitivity analyses undertaken by the ERG suggest that the ICER may be markedly higher when a mix of different (less expensive) TKIs is included as first-line treatment for distant metastases in the active monitoring group, and when alternative parametric survival models are applied to the probabilities of experiencing loco-regional and distant recurrence.

The ERG notes that longer-term follow-up of ADAURA may help to resolve some of the uncertainty surrounding the expected survival advantage for osimertinib.

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8 APPENDICES

Technical Appendix

All ERG exploratory analyses were undertaken in the company's updated model.

ERG exploratory analysis 1: Fix remaining model errors

a. weighted survival model for general population mortality

The table below presents the per-cycle mortality risk from a weighted survival model based on the proportion of males and females in ADAURA at baseline. Copy the figures in the 'Mortaltiy risk' column of the below table into worksheet "TP Matrix Comp0", range H11:H531 and worksheet "TP Matrix Comp1", range H10:H530.

Age	Mortality risk
63.00	0.000648505164442925
63.08	0.000648487379666718
63.17	0.000648469596962520
63.25	0.000648451816329776
63.33	0.000648434037769818
63.42	0.000648416261282314
63.50	0.000648398486868151
63.58	0.000648380714527219
63.67	0.000648362944260406
63.75	0.000648345176067822
63.83	0.000648327409949800
63.92	0.000700000469434636
64.00	0.000699980365037600
64.08	0.000699960263140453
64.17	0.000699940163743529
64.25	0.000699920066847604
64.33	0.000699899972452900
64.42	0.000699879880560084
64.50	0.000699859791169821
64.58	0.000699839704282001
64.67	0.000699819619897846
64.75	0.000699799538017243
64.83	0.000699779458641303
64.92	0.000769483459238662
65.00	0.000769459298473607
65.08	0.000769435141017127
65.17	0.000769410986870445
65.25	0.000769386836034003
65.33	0.000769362688508579
65.42	0.000769338544294951
65.50	0.000769314403393562
65.58	0.000769290265805522
65.67	0.000769266131531277
65.75	0.000769242000571380
65.83	0.000769217872927164
65.92	0.000836448304707749
66.00	0.000836414751476444
66.08	0.000836381203688008
66.17	0.000836347661344217
66.25	0.000836314124446402
66.33	0.000836280592995675
66.42	0.000836247066993701
66.50	0.000836213546441478
66.58	0.000836180031340783
66.67	0.000836146521692727
66.75	0.000836113017498641
66.83	0.000836079518760080
66.92	0.000911458891601269
67.00	0.000911420976669075
67.08	0.000911383068314509
67.17	0.000911345166539124
67.25	0.000911307271345030
67.33	0.000911269382733226
67.42	0.000911231500706267
67.50	0.000911193625265483
67.58	0.000911155756412541
67.67	0.000911117894149438
67.75	0.000911080038477396
67.83	0.000911042189398747
67.92	0.000999826348760169
68.00	0.000999782951765060
68.08	0.000999739562876023
68.17	0.000999696182094834
68.25	0.000999652809424045
68.33	0.000999609444865657
68.42	0.000999566088422221
68.50	0.000999522740095848
68.58	0.000999479399888537
68.67	0.000999436067803061
68.75	0.000999392743841310
68.83	0.000999349428005392
68.92	0.001095266694254530
69.00	0.001095213430112320
69.08	0.001095160177066790
69.17	0.001095106935121600
69.25	0.001095053704279980
69.33	0.001095000484545470
69.42	0.001094947275921520
69.50	0.001094894078411230
69.58	0.001094840892017950
69.67	0.001094787716744980
69.75	0.001094734552596010
69.83	0.001094681399573920
69.92	0.001187336461686780
70.00	0.001187285748038610
70.08	0.001187235044776360
70.17	0.001187184351903240
70.25	0.001187133669422470
70.33	0.001187082997336720
70.42	0.001187032335649320
70.50	0.001186981684362820
70.58	0.001186931043480780
70.67	0.001186880413005740
70.75	0.001186829792941050
70.83	0.001186779183289690
70.92	0.001289758366421090
71.00	0.001289686966110760
71.08	0.001289615583278110
71.17	0.001289544217929370
71.25	0.001289472870069970
71.33	0.001289401539706360
71.42	0.001289330226844300
71.50	0.001289258931489350
71.58	0.001289187653647720
71.67	0.001289116393325070
71.75	0.001289045150527630
71.83	0.001288973925260730
71.92	0.001453588546234670
72.00	0.001453514042085380
72.08	0.001453439556725940
72.17	0.001453365090162250
72.25	0.001453290642401070
72.33	0.001453216213448410
72.42	0.001453141803310910
72.50	0.001453067411994800
72.58	0.001452993039506190
72.67	0.001452918685851850
72.75	0.001452844351037650
72.83	0.001452770035070050
72.92	0.001657529674420450
73.00	0.001657430807233570
73.08	0.001657331969022400
73.17	0.001657233159798150
73.25	0.001657134379571820
73.33	0.001657035628354620
73.42	0.001656936906157090
73.50	0.001656838212990670
73.58	0.001656739548866360
73.67	0.001656640913794690
73.75	0.001656542307787220
73.83	0.001656443730854270
73.92	0.001830665286487680
74.00	0.001830545888087730
74.08	0.001830426528528720
74.17	0.001830307207826400
74.25	0.001830187925996980
74.33	0.001830068683056020
74.42	0.001829949479019380
74.50	0.001829830313902710
74.58	0.001829711187722350
74.67	0.001829592100493160
74.75	0.001829473052231470
74.83	0.001829354042952370
74.92	0.002047160818535290
75.00	0.002047012776716040
75.08	0.002046864789110870
75.17	0.002046716855743650
75.25	0.002046568976638350
75.33	0.002046421151818630
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75.50	0.002046125665132290
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75.75	0.002045682842841120
75.83	0.002045535344235460
75.92	0.002045387900081350
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76.25	0.002304707102862010
76.33	0.002304529973807920
76.42	0.002304352916871480
76.50	0.002304175932085210
76.58	0.002303999019483080
76.67	0.002303822179098300
76.75	0.002303645410963730
76.83	0.002303468715113110
76.92	0.002583230162449320
77.00	0.002583031205520840
77.08	0.002582832335199070
77.17	0.002582633551524880
77.25	0.002582434854540130
77.33	0.002582236244286220

77.42	0.002582037720803790
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77.58	0.002581640934319560
77.67	0.002581442671399480
77.75	0.002581244495414860
77.83	0.002581046406406220
77.92	0.002919496160485040
78.00	0.002919259357044400
78.08	0.002919022667623340
78.17	0.002918786092279580
78.25	0.002918549631069740
78.33	0.002918313284051570
78.42	0.002918077051281330
78.50	0.002917840932816110
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78.67	0.002917369039026060
78.75	0.002917133263813820
78.83	0.002916897603131300
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79.00	0.003245261930385990
79.08	0.003244983072899890
79.17	0.003244704363497550
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81.42	0.004096996402543350
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86.92	0.007735682461703420
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93.17	0.017494978168869100
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93.42	0.017490003621552500
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93.83	0.017481774426760200
93.92	0.017480137843164000
94.00	0.019601883202312000
94.08	0.019599822940584900
94.17	0.019597767064703500
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94.33	0.019593668467531300
94.42	0.019591625744632700
94.50	0.019589587404366300
94.58	0.019587553445795000
94.67	0.019585523867930200
94.75	0.019583498669730900
94.83	0.019581477850103400
94.92	0.019579461407903100
95.00	0.022053927818536000
95.08	0.022051901765291600
95.17	0.022049880151528800
95.25	0.022047862975868100
95.33	0.022045850236879300
95.42	0.022043841933079500
95.50	0.022041838062935100
95.58	0.022039838624860900
95.67	0.022037843617220900
95.75	0.022035853038328400
95.83	0.022033866886446500
95.92	0.022031885159787700
96.00	0.024532835744978200
96.08	0.024530314192158700
96.17	0.024527799035057300
96.25	0.024525290270405600
96.33	0.024522787894844600
96.42	0.024520291904925400
96.50	0.024517802297109600
96.58	0.024515319067770700
96.67	0.024512842213192800
96.75	0.024510371729573200
96.83	0.024507907613021200
96.92	0.024505449859560900
97.00	0.026328788883095600
97.08	0.026326072483607400
97.17	0.026323363528565100
97.25	0.026320662012620000
97.33	0.026317967930313800
97.42	0.026315281276079600
97.50	0.026312602044243200
97.58	0.026309930229022400
97.67	0.026307265824529800
97.75	0.026304608824771500
97.83	0.026301959223649800
97.92	0.026299317014962500
98.00	0.028992225487630800
98.08	0.028989781881698500
98.17	0.028987344897579800
98.25	0.028984914529546200
98.33	0.028982490771785800
98.42	0.028980073618402500
98.50	0.028977663063418600
98.58	0.028975259100773300
98.67	0.028972861724324100
98.75	0.028970470927849500
98.83	0.028968086705045500
98.92	0.028965709049529700
99.00	0.031626477590031000
99.08	0.031618727148188700
99.17	0.031611015670988800
99.25	0.031603343085047800
99.33	0.031595709315498000
99.42	0.031588114286010600
99.50	0.031580557918816200
99.58	0.031573040134726900
99.67	0.031565560853157000
99.75	0.031558119992145300
99.83	0.031550717468374900
99.92	0.031543353197196900
100.00	0.035253024887053400
100.08	0.035249365003488200
100.17	0.035245718654291600
100.25	0.035242085816926000
100.33	0.035238466468630600
100.42	0.035234860586424800
100.50	0.035231268147111400
100.58	0.035227689127279000
100.67	0.035224123503303600
100.75	0.035220571251352600
100.83	0.035217032347386300
100.92	0.035213506767162000
101.00	0.035209994486234400
101.08	0.035206495479960200
101.17	0.035203009723499700
101.25	0.035199537191818700
101.33	0.035196077859693300
101.42	0.035192631701709500
101.50	0.035189198692268300
101.58	0.035185778805586300
101.67	0.035182372015700000
101.75	0.035178978296465800
101.83	0.035175597621566000
101.92	0.035172229964507400
102.00	0.035168875298627000
102.08	0.035165533597092600
102.17	0.035162204832905200
102.25	0.035158888978903400
102.33	0.035155586007763300
102.42	0.035152295892001900
102.50	0.035149018603980700
102.58	0.035145754115905800
102.67	0.035142502399832400
102.75	0.035139263427665800
102.83	0.035136037171164500
102.92	0.035132823601942000
103.00	0.035129622691469500
103.08	0.035126434411077900
103.17	0.035123258731960900
103.25	0.035120095625176000
103.33	0.035116945061648200
103.42	0.035113807012171000
103.50	0.035110681447409600
103.58	0.035107568337902200
103.67	0.035104467654063600
103.75	0.035101379366186400
103.83	0.035098303444442600
103.92	0.035095239858887700
104.00	0.035092188579462100
104.08	0.035089149575991100
104.17	0.035086122818190800
104.25	0.035083108275668100
104.33	0.035080105917922000
104.42	0.035077115714348100
104.50	0.035074137634238900
104.58	0.035071171646786500
104.67	0.035068217721084800
104.75	0.035065275826130600
104.83	0.035062345930827900
104.92	0.035059428003987000
105.00	0.035056522014328900
105.08	0.035053627930486100
105.17	0.035050745721004800
105.25	0.035047875354347500
105.33	0.035045016798894400
105.42	0.035042170022944400
105.50	0.035039334994719700
105.58	0.035036511682364800
105.67	0.035033700053950700
105.75	0.035030900077475300
105.83	0.035028111720865500
105.92	0.035025334951980800
106.00	0.035022569738612100
106.08	0.035019816048486400
106.17	0.035017073849266700
106.25	0.035014343108555600
106.33	1.000000000000000000

b. Utility losses associated with AEs assumed to last for 1 year

In worksheet "Results", divide the formula in cells J12, J20, J30 and J38 by 'cycles_per_year'

c. Incorrect proportions of CNS recurrences

In worksheet "Settings", replace cell J60 with 28.6% and J61 with 34.4%

All remaining exploratory analyses include these corrections.

ERG exploratory analysis 2: Re-treatment not permitted

In worksheet "Settings", select 'No' from the drop down menu in cell J35

ERG Exploratory Analysis 3: Treatment effects for osimertinib in DM1 capped at 5 years

In worksheet "TP Matrix Comp0", set cells "R71:R531" equal to "O71:O531".

In worksheet "TP Matrix Comp1", set cells "O70:O530" equal to worksheet "STM_Surv" cells "R74:R534"

ERG exploratory analysis 4: Update unit costs for administration of chemotherapy and docetaxel drug acquisition

The updated costs of day case chemotherapy administration and docetaxel acquisition costs are shown below:

Resource	Unit Cost	Source
Administration of chemotherapy, first cycle	£385.28	NHS Reference Costs. Daycase and Reg Day/night. Service code SB14Z- Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
Administration of chemotherapy, subsequent cycles	£362.35	NHS Reference Costs. Daycase and Reg Day/night. Service code SB15Z- Deliver Subsequent Elements of a Chemotherapy Cycle
Docetaxel acquisition costs	£12.50	eMIT 2020

The total updated costs for administration and monitoring of PDC, pemetrexed, cisplatin and ABCP is £391.54 for the initial visit and £368.61 for subsequent visits. The total updated costs for administration and monitoring of docetaxel are £392.81 and £369.88, initial and subsequent visits respectively.

On worksheet "Drug costs":

- Set cells I121 and I123:125 to £391.54
- Set cell I122 to £392.81
- Set cells K121 and K123:125 to £368.61
- Set cell K122 to £369.88
- Set cells M62 and M73 to £12.50

A further model correction is required in cells N117:127 as the formulae use refer to columns J instead of K, and vice versa.

ERG exploratory analysis 5: Inclusion of wastage for osimertinib (0.50 packs)

1. In worksheet "Trace Comp0", cell AI9, enter the following formula and drag down to cell AI43:
   =(J9-J10) * 0.5 * cost_drug_acquisition_dfs_tx0
2. In worksheet "TP Matrix Comp0", cell AQE9, enter the following formula:
   =SUM(AQF11:AQF531)*0.5*cost_drug_acquisition_dm1_tx0_retreatment
3. In worksheet "TP Matrix Comp1", cell WH8, enter the following formula:
   =SUM(WI10:WI530)*0.5*cost_drug_acquisition_dm1_tx1
4. In worksheet "Results", cells M13 and M21, add the following to the end of the existing formula "+SUM('Trace Comp0'!AI9:AI43)+'TP Matrix Comp0'!AQE9"
5. In worksheet "Results", cells M31 and M39, add the following to the end of the existing formula: "+'TP Matrix Comp1'!WH8"

ERG exploratory analysis 6: Inclusion of ABCP treatment option

In worksheet "Settings", cell J66, select IMPower form the drop down menu

ERG exploratory analysis 7: 8-year cure point applied

In worksheet "Settings", set cell J44 to 96

ERG exploratory analysis 8: ERG's preferred base case 1, optimistic scenario

The ERG's preferred base case 1 includes ERG exploratory analysis 1-7; therefore, apply changes 1-6 listed above.

ERG exploratory analysis 9: ERG's preferred base case 2, pessimistic scenario

The ERG's preferred base case includes ERG exploratory analysis 1-7 therefore, apply all the changes listed above.

ERG Additional Sensitivity Analyses

All of the following additional sensitivity analyses are run on both ERG exploratory analyses 8 and ERG exploratory analyses 9.

Additional sensitivity analysis 1: Use of utility values from Andreas *et al.*[14]

In worksheet "Utilities":

- Set cell F14 to 0.72
- Set cell F24 to 0.62
- Set cells F34:F38 to 0.59

Additional sensitivity analysis 2: Adjuvant osimertinib QALY loss extended to 1-year

In worksheet "Results", in cells J12 and J20, remove '/cycles_per_year' from the formula.

Additional sensitivity analysis 3: Inclusion of mix of TKIs in DM1 in active monitoring group

Update mix of TKIs in first-line treatment of metastases, placebo group. In worksheet "Clinical inputs":

- Set cell T25 to [redacted]
- Set cell T26 to [redacted]
- Set cell T27 to [redacted]
- Set cell T28 to [redacted]
- Set cell T29 to [redacted]

Update mix of TKIs in second-line treatment of metastases, placebo group. In worksheet "Clinical inputs":

- Set cell T56 to [redacted]
- Set cell T57 to [redacted]

ERG Additional Sensitivity Analysis 4: Use of log-normal model for TP (DF to DM1)

4a. In worksheet "STM_Surv", select 'log normal' from the drop down menus in cells BO16 and BP16

4b. In worksheet "STM_Surv", select 'log normal' from the drop down menu in cell BO16 only

ERG Additional Sensitivity Analysis 5: Use of log-logistic for TP1 (DF to LR) and log-normal for TP2 (DF to DM1), treatment arm only

This analysis is implemented only for the ERGs preferred pessimistic analysis (EA9). In worksheet "STM_Surv", select 'log-logistic' from the drop down menu in cell BI16 and 'log-normal'in the drop down menu in cell BO16.

ERG Additional Sensitivity Analysis 6: EGFRm test cost halved

In worksheet "Other costs", set cell H16 equal to 5.

ERG Additional Sensitivity Analysis 7: Re-treatment with osimertinib included

In worksheet "Settings", select 'Yes' from the drop down menu in cell J35.

ERG Additional Sensitivity Analysis 8: Alternative proportions receiving whole brain radiotherapy for CNS metastases

In worksheet "DM costs", set cell H145 to 66% and cell H146 to 34%

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small cell lung cancer after complete tumour resection [ID3835]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by the end of **12TH April,** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Table 1. Company's revised "ERG report Table 49"

Additional sensitivity analysis	Optimistic scenario - cure point at 5 years			Pessimistic scenario - cure point at 8 years for osimertinib, placebo at 5 years		
	Inc. QALYs	Inc. costs	ICER	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis	[redacted]	[redacted]	**£9,979**	[redacted]	[redacted]	**£20,417**
ASA1: Use of utilities from Andreas	[redacted]	[redacted]	**£10,467**	[redacted]	[redacted]	**£21,032**
ASA2: Assume AE QALY loss for one year for adjuvant osimertinib	[redacted]	[redacted]	**£9,988**	[redacted]	[redacted]	**£20,442**
ASA3a: Different mix of TKIs ([redacted]% treated with osimertinib)	[redacted]	[redacted]	**£19,390**	[redacted]	[redacted]	**£33,327**
ASA3a: Different mix of TKIs (80% treated with osimertinib)	[redacted]	[redacted]	**£16,439**	[redacted]	[redacted]	**£29,389**
ASA4a: Use log-normal for TP2 (DF to DM1) in both arms, adjusted hazards	[redacted]	[redacted]	**£9,326**	[redacted]	[redacted]	**£25,544**
ASA4b: Use log-normal for TP2 (DF to DM1) in treatment arm only	[redacted]	[redacted]	**£13,224**	[redacted]	[redacted]	**£38,897**
ASA5: Use log-logistic for TP1 (DF to LR) and log-normal for TP2 (DF to DM1), treatment arm only	Not applicable			[redacted]	[redacted]	**£54,913**
ASA6: Halve EGFR testing cost to account for some tests already	[redacted]	[redacted]	**£9,818**	[redacted]	[redacted]	**£20,185**
ASA7: Allow re-treatment with osimertinib	[redacted]	[redacted]	**£10,808**	[redacted]	[redacted]	**£22,989**
ASA8: Alternative proportion of patients receiving whole-brain radiotherapy for CNS metastases	[redacted]	[redacted]	**£9,857**	[redacted]	[redacted]	**£20,280**

Abbreviations: QALY, quality-adjusted life year; ICER , incremental cost,-effectiveness ratio; Inc. , incremental; ASA , additional sensitivity analysis; DF – disease-free; LRR , locoregional recurrence; DM1, first-line distant metastasis; CNS , central nervous system; TKI , tyrosine kinase inhibitor; EGFR , epidermal growth factor receptor

Table 2. Abbreviations

AIC	Academic in confidence
ASA	Additional sensitivity analyses
BIC	Bayesian information criterion
CIC	Commercial in confidence
CS	Company submission
DF	Disease free
DFS	Disease-free survival
DM	Distant metastasis
DSU	Decision support unit
EGFR	Epidermal growth-factor receptor
EGFRm	Epidermal growth-factor receptor mutation
EGFR-TKI	Epidermal growth-factor receptor tyrosine kinase inhibitor
ERG	Evidence Review Group
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KM	Kaplan-Meier
EGFR	Epidermal growth-factor receptor
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
PAS	Patient access scheme
QALY	Quality adjusted life year
SoC	Standard of care
TKI	Tyrosine kinase inhibitor
UK	United Kingdom

Company Issue 1 ERG Additional Sensitivity Analysis 3 is a factually incorrect analysis as it is informed by superseded prescribing data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Additional Sensitivity Analysis 3 **Section 1.5, Page 15,** **Section 5.4.1, Page 130:** ERG Additional Sensitivity Analysis 3: Inclusion of mix of TKIs in DM1 in active monitoring group	The Company believe that ERG ASA3 (DM1 subsequent treatment with osimertinib in 48.9% of patients in active monitoring arm) is factually inaccurate as the data informing this analysis is now out-of-date. The Company request that this analysis is updated to accurately reflect the current usage of osimertinib in metastatic NSCLC.	**ERG ASA3 is factually incorrect as it is informed by national prescribing data that is now superseded.** At ERG clarification questions, the Company provided prescribing data from Q4 2020 which demonstrated that [redacted]% patients in the 1L mNSCLC disease setting received treatment with osimertinib. This was the most up to date data available at the time of clarification questions. The Company noted in response to ERG clarification question B2 that the use of osimertinib in the 1L metastatic setting will continue to rapidly increase. As osimertinib was recently recommended by NICE for 1L treatment of metastatic disease (NICE TA654, October 20201), it is expected that its use will continue to increase as more newly diagnosed patients with metastatic disease are treated with osimertinib. National Hospital Pharmacy Audit data (Figure 1) demonstrates that the usage of osimertinib	This is not a factual inaccuracy. The analysis presented in the original ERG report was based on the data provided by the company in their clarification response. We have updated ASA3 to reflect the company's updated estimates of the current use of osimertinib ([redacted] in DM1 and [redacted] in DM2). It should be noted that the ERG's preferred analysis retain the company's base case assumption that all patients in the active monitoring group receive osimertinib as first-line treatment for distant metastases.

		in metastatic disease was rapidly increasing towards the end of 2020. **Figure 1. EGFR-TKIs market shares**  Abbreviations: Rolling Q, rolling quarter Whilst still premature, more recent national prescribing data from Q1 2021 demonstrates a continued increase in the market share for osimertinib, with [redacted]% patients receiving a TKI receiving treatment with osimertinib; thereby representing a ~[redacted]% share increase since the last quarter. This pattern has been observed in other countries where Tagrisso has launched/been reimbursed earlier than in the UK and therefore more mature prescribing	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
		data are available to inform longer term estimates. For example, data from Italy, Spain and Japan clearly demonstrates a significant increase in the use of osimertinib following formal reimbursement. In all cases, there is a steady increase in the share of osimertinib, with a current peak or approximately [redacted]. This provides further evidence to support the unanimous view from clinicians who state that osimertinib is the standard of care for all newly diagnosed patients (see Figures 5 to 7 in Appendix A). **Company's revised ASA3** In line with other recent NICE appraisals (e.g. acalabrutinib in untreated CLL, NICE ID1613), the likely current share of subsequent treatments (i.e. osimertinib in 1L metastatic disease) should be used as the basis for decision making. Based on clinician feedback and recent prescribing trends, the Company believe this estimate to be close to 90-95%. The Company conducted two exploratory analyses that conservatively assume [redacted]% and 80% of patients in the active monitoring arm receive treatment with osimertinib in DM1. The remaining proportion of patients in DM1 are assumed to receive other EGFR-TKIs (erlotinib, gefitinib, afatinib or dacomitinib) and relative proportions were informed by IQVIA national prescribing data.The proportions per treatment used in these analyses are provided in Table 3.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Table 3. Company's revised ASA3 – DM1 treatment mix (active monitoring arm)

Scenario		Health state	Treatm
[redacted]% of DM1 treated with osimertinib	DM1	Osimertinib: [redacted]%	[redacted]
	DM2	[redacted]	[redacted]
80% of DM1 treated with osimertinib	DM1	Osimertinib: 80%	[redacted]
	DM2	[redacted]	[redacted]

The cost-effectiveness analysis results for the ERG's optimistic scenario and pessimistic scenario are presented in Table 4.

Table 4. Company's revised ASA3 – results

	Optimistic scenario			Pessimistic scenario		
	Inc. QALYs	Inc. costs	ICER	Inc. QALYs	Inc. costs	ICER

Description of problem	Description of proposed amendment	Justification for amendment							ERG response
		[redacted]% of DM1 treated with osimertinib	[redacted]	[redacted]	**£19,390**	[redacted]	[redacted]	**£33,327**	
		80% treated with osimertinib	[redacted]	[redacted]	**£16,439**	[redacted]	[redacted]	**£29,389**	

Company Issue 2 ERG Additional Sensitivity Analyses 4a

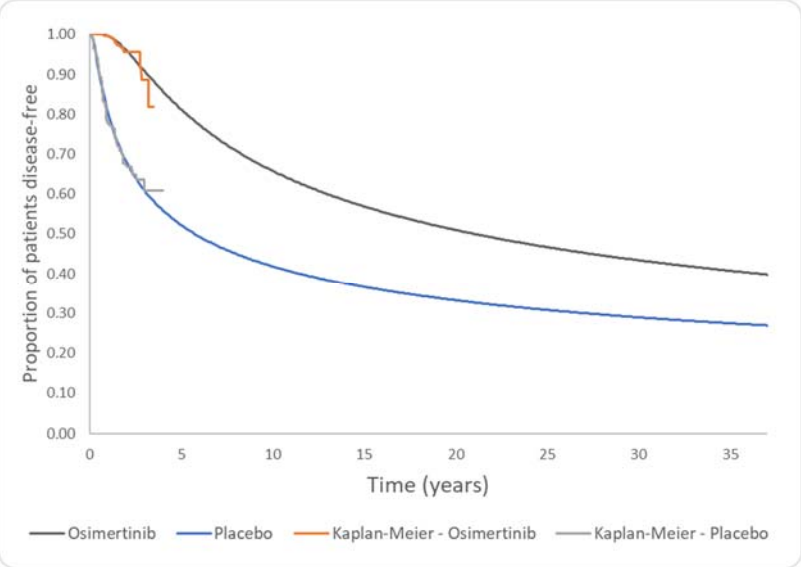
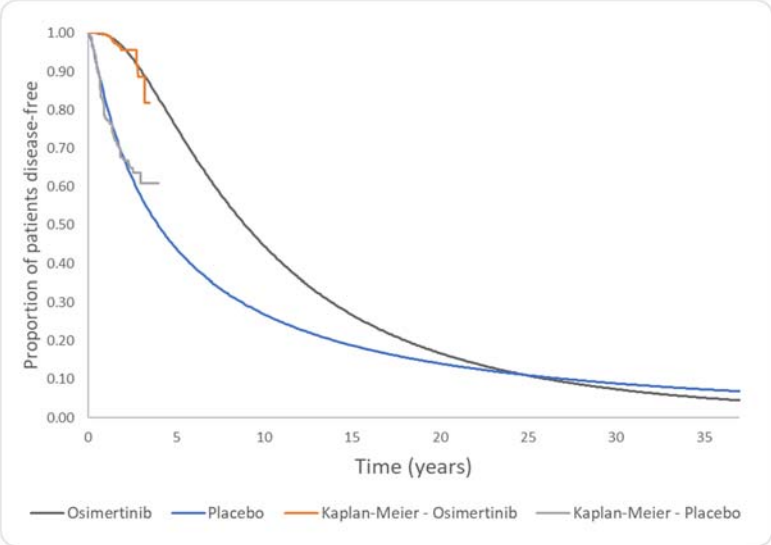
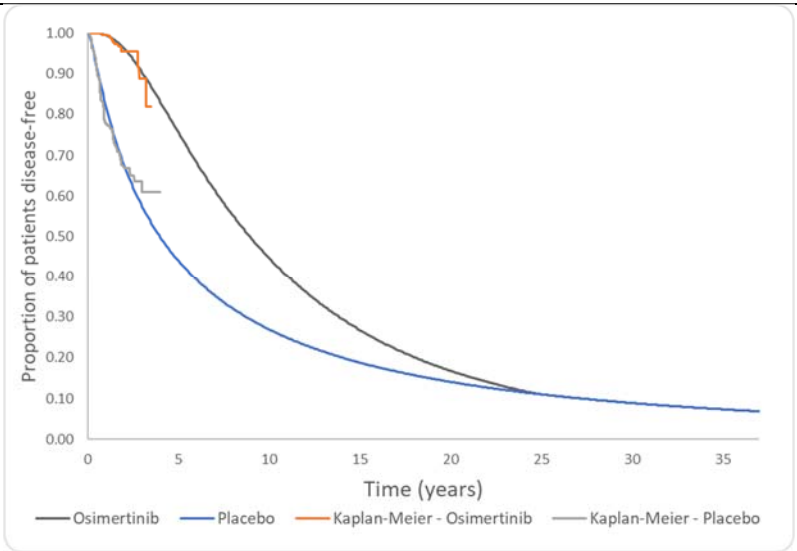
Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.4.1, Page 130: **"**ERG Additional Sensitivity Analysis 4: Use of log-normal model for TP2 (DF to DM1) "	The Company ask that the ERG amend the hazards in ASA4a so that the survival curves for the two arms do not cross, to avoid clinical implausibility.	**ERG ASA4a produces extrapolated curves for TP2 (DF to DM1) that are methodologically flawed as the curves for adjuvant osimertinib and active monitoring (placebo) arms cross** When the log-normal model is selected for TP2 in both arms, the curves for osimertinib and placebo cross at approximately 22 years into the model time horizon. After this time point, the cumulative probability of remaining disease free is greater in the active monitoring arm than in the osimertinib arm, which is not clinically plausible as it directly undermines data from the ADAURA trial. [1] **Figure 2. Extrapolations for DF to DM1 (TP2) – both arms: generalised gamma**  	This is not a factual inaccuracy. The predicted transition probabilities presented in the company's fact check response ignore the fact that the company's economic model applies cure assumptions which reduce the predicted risks of relapse from the parametric survival models by 95%. As such, the problem of crossing curves shown in Figure 3 does not apply in the economic model. On a related point, we note that in ASA5, the risk of relapse following the cure timepoint is higher for the adjuvant osimertinib group than the active monitoring group. This may not be considered plausible. However, the absolute risk in both groups is very low and setting the cure-related risk reduction parameter to 100% has virtually no impact on the model results. The report has not been amended in response to the company's comment.

Figure 3. Extrapolations for DF to DM1 (TP2) – both arms: log-normal



The pattern of long-term disease recurrence produced in this analysis lacks clinical and methodological validity. Therefore, if the log-normal model is selected for TP2, the hazards for this transition should be amended so that after ~22 years, the risk of recurrence for both arms is set to be equal. This is a conservative yet more plausible assumption than the scenario presented by the ERG.

Figure 4. Extrapolations for DF to DM1 (TP2) – both arms: log-normal, adjusted hazards

		 Results for the Company's revised ASA 4a are included in Table 1..	

Company Issue 3 Clarification regarding the assumption of no retreatment with osimertinib in the adjuvant osimertinib arm

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, Page 12; **Section 1.4, Page 15;** **Section 1.5, Page 17;** **Section 2.2.2, Page 25;** **Section 2.2.4, Page 29;** **Section 5.3.4, Page 107;** **Section 5.3.4, Page 115;** **Section 5.3.4, Page 121:** "Re-treatment with osimertinib for distant metastases is assumed, yet personal communication received from NHS England (NHSE) indicates that this will not be permitted."	The Company ask the ERG provide further information on the personal communication received from the NHSE that indicates that retreatment would not be permitted.	Amendments to the Company's base case that are included in the ERG's preferred analysis need to be made on data or information that is made available to the Company. The Company therefore requests that the rationale underpinning this statement made by NHSE is provided.	This is not a factual inaccuracy. The personal communication was received from NHSE via NICE. NHSE may be able to provide further information during the technical engagement stage. The report has not been amended.

Company Issue 4 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.3, Page 12: "Neither treatment group includes the four-drug reimen of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) for the second-line treatment of distant metastases"	To update the text as follows: "Neither treatment group includes the four-drug ~~reimen~~ regimen of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) for the second-line treatment of distant metastases"	Typographical error – spelling	This typo has been corrected
Section 1.5, Page 14: "The model also assumes that under current practice, all patients who develop distant metastases would receive osimertinib in the first-line setting (in DM1)."	To update the text as follows: "The model also assumes that all patients who receive active monitoring (placebo) who develop distant metastases would receive osimertinib in the first-line setting (in DM1)."	It is not immediately clear to the reader that this only applies to the active monitoring arm.	We believe this is already clear, but have amended the text to ensure clarity
Section 1.5, Page 16: The ERG's additional sensitivity analysis including alternative parametric survival models for TP1 and TP2 leads to a higher deterministic ICER of £54,913 per QALY gained.	To update the text as follows: "The ERG's highly pessimistic additional sensitivity analysis including alternative parametric survival models for TP1 and TP2 leads to a higher deterministic ICER of £54,913 per QALY gained."	To maintain consistency – this analysis is noted as highly pessimistic in Section 5.4.1 and Section 5.4.2.	The text has been amended as requested

Section 2.1.1, Page 21: "The total annual incidence of patients in England and Wales with EGFRm-positive NSCLC who are stage IB−IIIA, have undergone complete surgical resection, and who are eligible for adjuvant therapy is estimated in the CS to be 386, reaching a total of 485 incident patients after 5 years. The basis for these estimates is not presented in the CS."	To update the text as follows: "According to the Company's budget impact analysis, the total annual incidence of patients in England and Wales with EGFRm-positive NSCLC who are stage IB−IIIA, have undergone complete surgical resection, and who are eligible for adjuvant therapy is estimated in the CS to be 386, reaching a total of 485 incident patients after 5 years."	Missing information – These estimates were sourced from the CS budget impact analysis.	This is not a factual inaccuracy. The company's budget impact analysis is not cited in the CS. However, for clarity, the following text has been added to this section of the ERG report: "The basis for these estimates is not presented in the CS. The company's factual accuracy response clarifies that these estimates are based on the company's budget impact analysis."
Section 3.0, Page 33, Table 3: The ERG requested a subgroup analysis to assess the cost-effectiveness of osimertinib for patients with stage 1B disease; however, the company did not present this analysis (see Section 3.6)	To update the text as follows: "The ERG requested a subgroup analysis to assess the cost-effectiveness of osimertinib for patients with stage 1B disease; however, the company did not present this analysis as data are currently very limited. (see Section 3.6)"	To maintain consistency with Section 1.5, Page 19 which accurately notes the Stage IB subgroup analysis was not provided by the Company due to very limited data.	This is not a factual inaccuracy. However, the text has been amended as requested.
Section 4.2.3, Page 49, Table 10:	To update the text as follows:	The 99.12% confidence intervals for the DFS hazard ratios for Stage IB, II and IIIA subgroups were not provided	The text has been amended as requested,

"Table 10 DFS by stage (adapted from CS, page 53 and Table 12)"	"Table 10 DFS by stage (adapted from CS, page 53, Table 12 and Wu et al. 2020)"	in the CS but are available in Wu et al. 2020.	
Section 5.2.4, Page 95: "The model asuumes that patients re-treated with osimertinb do not require re-testing for EGFR mutations"	To update the text as follows: "The model ~~asuumes~~ assumes that patients re-treated with ~~osimertinb~~ osimertinib do not require re-testing for EGFR mutations"	Typographical error – spelling	These typos have been corrected
Section 5.1.1, Page 59: "The company performed systematic literature searches for (i) published cost-effectiveness studies of patients who have stage IB-111A NSCLC;"	To update the text as follows: "The company performed systematic literature searches for (i) published cost-effectiveness studies of patients who have stage IB-IIIA NSCLC;"	Typographical error	The text has been amended as requested
Section 5.3.1, Page 101, Table 40: The total costs in the active monitoring arm and ICERs for the Company's model are from the ERG's double-programmed model and vice versa.	Please update this table with the correct results for the Company's model; total costs in the active monitoring arm ([redacted]) and ICER (£12,489).	Typographical error	The headings have been switched
Section 5.3.2, Page 102:	To update the text as follows:	Typographical error – spelling	This typo has been corrected

"For example, the model cost for subsequent oncology visits is based on the weighted average for consultant-led outpatient attendance for clinical oncology including: admitted and non-admitted; face-to-face and non-face-to-face; follow-up and first visits; multi-professional and single consultant-led attenances"	"For example, the model cost for subsequent oncology visits is based on the weighted average for consultant-led outpatient attendance for clinical oncology including: admitted and non-admitted; face-to-face and non-face-to-face; follow-up and first visits; multi-professional and single consultant-led ~~attenances~~ attendances"		
Section 1.5, Page 16: "The ERG's additional sensitivity analysis including alternative parametric survival models for TP1 and TP2 leads to a higher deterministic ICER of £54,913 per QALY gained."	To update the text as follows: "The ERG's **highly pessimistic** additional sensitivity analysis including alternative parametric survival models for TP1 and TP2 leads to a higher deterministic ICER of £54,913 per QALY gained."	The references to ERG Additional Sensitivity Analysis 5 in the report are inconsistent. To avoid misleading the reader it should be made explicitly clear that this is a highly pessimistic analysis, as noted by the ERG in Section 5.4.1, Page 131.	This point was raised earlier in this table and has already been addressed.
Section 5.5, Page 137: "In addition, the ICER increases markedly when a mix of different (less expensive) TKIs is included as first-line treatment for	To update the text as follows: "In addition, the ICER increases markedly when a mix of different (less expensive) TKIs is included as first-line treatment for distant metastases in the active	The references to ERG Additional Sensitivity Analysis 5 in the report are inconsistent. To avoid misleading the reader it should be made explicitly clear that this is a highly	The ERG agrees that ASA5 is highly pessimistic. However, ASA4a and 4b, which this point also refers to, are not necessarily highly pessimistic. The report has

distant metastases in the active monitoring group, and when alternative parametric survival models are applied to the probabilities of developing loco-regional and distant recurrence in the adjuvant osimertinib group.”	monitoring group, and when **highly pessimistic** alternative parametric survival models are applied to the probabilities of developing loco-regional and distant recurrence in the adjuvant osimertinib group.”	pessimistic analysis, as noted by the ERG in Section 5.4.1, Page 131.	not been amended in response to this comment.

References

1. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non–Small-Cell Lung Cancer. *New England Journal of Medicine.* 2020.

Appendix A

Figure 5. Trend in osimertinib 1L share in patients with EGFRm positive mNSCLC - Italy

Figure 6. Trend in osimertinib 1L share in patients with EGFRm positive mNSCLC – Japan

Figure 7. Trend in osimertinib 1L share in patients with EGFRm positive mNSCLC – Spain

NICE National Institute for Health and Care Excellence

Technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Thursday 20 May 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**AstraZeneca Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS	YES	**Disease-free survival (DFS) is a clinically relevant and accepted endpoint in resected epidermal growth factor receptor mutant (EGFRm) non-small cell lung cancer (NSCLC)** DFS measures the time, after complete surgical resection without recurrence, development of new cancer or death. The mainstay of treatment in resectable NSCLC is surgical resection. The main goal of treatment in this setting is to prolong the time in which the patient is cancer-free (i.e. extend disease-free survival). The European Society of Molecular Oncology (ESMO) and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines on lung cancer recommend treatment with curative intent for patients with early-stage NSCLC with the goal of extending the time spent living disease-free.[1,2] DFS, and its equivalents (event-free survival, recurrence-free survival) are considered highly relevant primary endpoints for clinical trials evaluating adjuvant treatments and have been accepted by regulators and health technology assessment bodies. All of the major randomised clinical trials of older generation adjuvant EGFR-TKIs (ADJUVANT/CTONG1104, RADIANT, SELECT, EVAN) reported DFS as the primary study endpoint. In addition, the European Medicines Agency (EMA) and the Institute for Quality and Efficiency in Health Care (IQWiG) guidelines advise determination of DFS as an appropriate outcome in clinical studies for adjuvant treatment.[3,4] DFS and its equivalents have also been accepted as the primary endpoint in prior NICE technology appraisals of adjuvant treatments in breast cancer and melanoma (TA569, TA632, TA612, TA544, TA684).[5-9] **There is significant intrinsic value in extending DFS in patients with resected EGFRm NSCLC** Despite the curative intent of surgery, post-surgical recurrence remains frequent (45–76% of patients with stage IB–III NSCLC recur within 5 years).[10] Furthermore, most post-resection recurrences are

Key issue	Does this response contain new evidence, data or analyses?	Response
		due to distant recurrence, which are responsible for a significant proportion of the symptom burden and deaths in these patients. The LuCaBis burden of illness study in European patients with completely-resected stage IB–IIIA NSCLC found distant metastases accounted for 68% of disease recurrence.[11] Brain metastases are also highly common, occurring in 40−50% of all patients with NSCLC and those with EGFRm-positive disease at twice-higher risk of brain metastases than patients with wild-type EGFR.[12-14] Brain metastases are associated with a significant neurological burden, with at least 10% of patients with EGFRm NSCLC brain metastases experiencing seizures, speech problems, focal neurologic deficits, drowsiness, and memory problems. Disease recurrence is also associated with impairments in a patient's quality of life, with distant metastases imposing more substantial impairments that locoregional recurrence. Brain metastases in particular are associated with vast decreases in health-related quality of life. Multiple studies have found patients with brain metastases reported deteriorations in European Organisation for Research and Treatment of Cancer quality of life questionnaire scores, emotional and social functioning. The declines in health-related quality of life experienced by patients with brain metastases are significantly faster than for those without brain metastases.[15,16] Therefore, there is a significant intrinsic value in extending disease-free survival as prolonging the time over which a patient is cancer-free will result in a lowered symptom burden by avoiding the debilitating symptoms of disease recurrence and improvements in health-related quality of life. Extending remission (disease-free survival) and thus the time to subsequent treatments provides patients with long-term benefits even in the absence of overall survival. The intrinsic value of DFS was confirmed by [redacted]

Key issue	Does this response contain new evidence, data or analyses?	Response
		[redacted] Osimertinib is associated with an unprecedented and highly statistically significant DFS benefit in the adjuvant setting. Osimertinib demonstrated an 80% reduction in risk of recurrence or death versus placebo in the overall trial population (hazard ratio [HR]: 0.20; 99.12% confidence interval [CI]: 0.14, 0.30; p<0.001). This unprecedented benefit was consistent across all patient subgroups. In patients who had a disease recurrence or progression, the majority experienced locoregional recurrences when treated with osimertinib (7% of patients in the osimertinib arm experienced locoregional recurrence), compared with a majority who experienced distant recurrence in the placebo group (23% of patients in the placebo arm experienced distant metastases). By significantly extending the disease-free period (and the time to subsequent treatment) in patients with resected EGFRm NSCLC, adjuvant osimertinib will provide patients with invaluable long-term benefits compared to existing active monitoring. **ADAURA DFS outcomes are consistent with real-world evidence** Interim results from the placebo arm of ADAURA are in line with real-world estimates of DFS in resected EGFRm NSCLC patients receiving active management. [redacted]

Key issue	Does this response contain new evidence, data or analyses?	Response
		[redacted] [redacted] [redacted] **Table 1: Patient characteristics EGFRm stage IB to IIIA NSCLC patients in PALEOS study**

Characteristic	Number of patients	Percentage (%)
Race		
East, Central or SE Asian	[redacted]	[redacted]
South Asian	[redacted]	[redacted]
Asian (unspecified)	[redacted]	[redacted]
Caucasian	[redacted]	[redacted]
Other	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Sex		
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
Age		
Mean Age at Diagnosis (SD) in years	[redacted]	

Key issue	Does this response contain new evidence, data or analyses?	Response

Median Age at Diagnosis (Min, Max) in years				
Stage at diagnosis				
IB				
II				
IIIA				
Recurrence				
Locoregional				
Metastatic				
No recurrence				
Result of Surgery				
R0 (complete resection)				
Median Follow-Up Time in Months (95% CI)				
Overall				
Stage IB				
Stage II				
Stage IIIA				

. A comparison of DFS outcomes is provided in Table 2.

Table 2: Comparison of real-world and ADAURA DFS outcomes in patients receiving active management

	Real-world study	ADAURA
Median DFS		
Stage IB-IIIA		27.5 months
Stage II-IIIA		19.6 months
Two-year DFS		
Stage IB-IIIA		52.4%
Stage II-IIIA		43.6%

Key issue	Does this response contain new evidence, data or analyses?	Response
		[redacted] **Adjuvant osimertinib is expected to result in a significant OS benefit** OS data from ADAURA is highly immature. However, a numerical benefit was observed in the overall population for osimertinib vs placebo (in total, 9 patients in the osimertinib arm and 20 patients in the placebo arm had died (2.7% and 5.8%, respectively). Despite the immaturity of the current OS data, clinicians interviewed by the Company [redacted] stated and agreed that adjuvant osimertinib is undoubtedly expected to translate into long-term survival benefits. This prediction is based on three key points: 1. The unprecedented magnitude of DFS benefit observed with osimertinib in ADAURA, which is greater than the DFS benefit observed with earlier generation EGFR-Tyrosine kinase inhibitors (TKIs) trialled in the adjuvant setting; 2. The reduced rate of recurrence with distant/ central nervous system (CNS) metastases observed with osimertinib versus placebo; 3. The benefits in OS and CNS recurrence with osimertinib vs first- and second-generation EGFR-TKIs in the metastatic NSCLC setting. **1: Osimertinib has demonstrated an unprecedented DFS benefit in adjuvant EGFRm NSCLC** Osimertinib is associated with an unprecedented and highly statistically significant DFS benefit in the adjuvant setting. Osimertinib demonstrated an 80% reduction in risk of recurrence or death versus placebo in the overall trial population (HR: 0.20; 99.12%, CI: 0.14, 0.30; p<0.001). This significant benefit was consistent across all patient subgroups.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Osimertinib is the first EGFR-TKI to demonstrate this magnitude of DFS benefit in this setting (HR: 0.20). A comparison of DFS observed with previous Phase III randomised controlled trials (RCTs) of first-generation EGFR-TKIs in the adjuvant setting is provided in Table 3.

Table 3: DFS results in Phase III RCTs on adjuvant first-generation EGFR TKIs in NSCLC
<table>
<tr><th>Study</th><th>NSCLC population</th><th>Treatment arms</th><th>DFS HR (95% CI)</th></tr>
<tr><td>ADJUVANT/ CTONG 1104[17,18]</td><td>Resected stage II–IIIA EGFRm</td><td>Gefitinib versus vinorelbine plus cisplatin</td><td>0.60 [0.42, 0.87]</td></tr>
<tr><td>RADIANT[19]</td><td>Resected stage IB–IIIA (EGFR-expressing/ amplified)</td><td>Erlotinib versus placebo</td><td>0.61 [0.38, 0.98]</td></tr>
<tr><td>BR19[20]</td><td>Resected stage IB–IIIA</td><td>Gefitinib versus placebo</td><td>1.84 [0.44, 7.73]</td></tr>
</table>

The DFS benefit observed in ADAURA was so great that the Independent Data Monitoring Committee (IDMC) recommended in April 2020 that the trial be unblinded two years early, after determination of overwhelming efficacy with osimertinib.[21] This early unblinding has resulted in the high immaturity of the DFS and OS data in this interim data cut. 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 interim analysis cut-off following IDMC recommendation, DFS events had occurred in 156 patients (33% maturity).

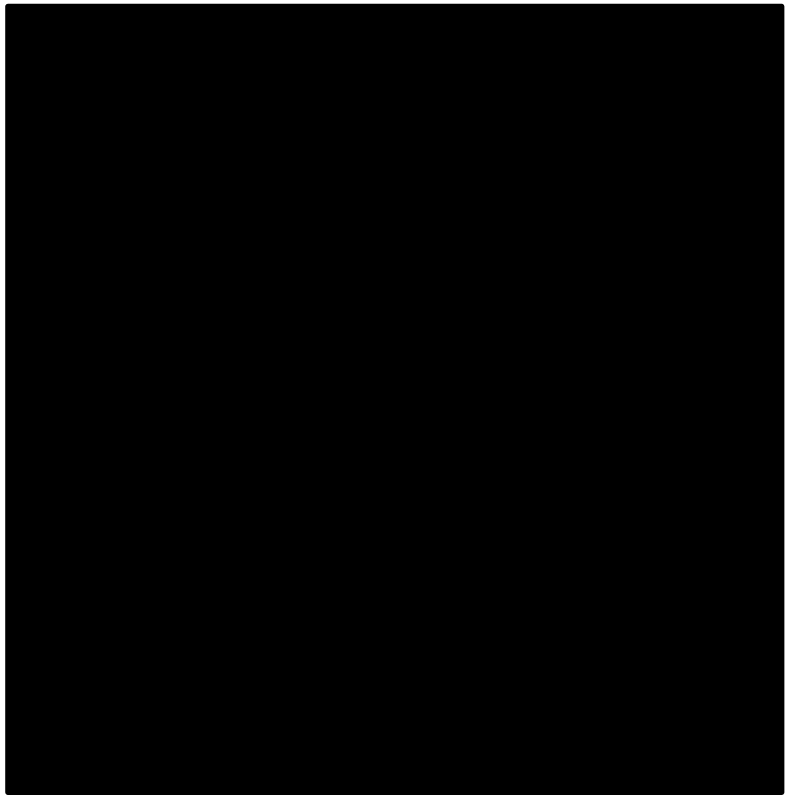
[redacted]

2: Osimertinib is associated with a significant reduction in CNS metastases
</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
		Currently, over 40% of NSCLC patients experience CNS metastases over their disease course, with a significantly higher risk in those with EGFRm disease. A recent study found that brain metastases accounted for 41% of disease recurrence in patients with completely-resected stage IB–IIIA NSCLC in the UK, France, and Germany.[11] CNS metastases have been found to be associated with significant reductions in long-term survival. A real-world study evaluating the impact of brain metastases in patients with EGFRm NSCLC found that median OS from metastatic diagnosis was significantly lower in patients with brain metastasis than patients without (11.9 months [95% CI: 9.7–13.4] vs 16.0 months [95% CI: 9.1–20.6], respectively; p = 0.017).[22] Despite CNS metastases being common in patients with EGFRm NSCLC, a clinically meaningful and statistically significantly lower risk of CNS recurrence or death was observed with osimertinib compared with placebo in the overall population: HR for CNS DFS was 0.18 (95% CI: 0.10, 0.33; p<0.0001), indicating an 82% reduction in the osimertinib arm compared with placebo. In the overall population (stage IB-IIIA), the proportion of patients experiencing CNS events was numerically lower with osimertinib (4 patients [1.2%]) vs placebo (33 patients [9.6%]). In addition to the unprecedented DFS benefit demonstrated, osimertinib is also the first EGFR-TKI in the adjuvant setting to demonstrate a significant improvement in CNS outcomes. First-generation TKIs showed little impact on the risk of CNS metastases in previous adjuvant trials. Prior to ADAURA, the greatest reduction in CNS metastases observed with an EGFR-TKI in the adjuvant setting was 26% (BR19). The poor CNS (and therefore OS) outcomes observed in previous clinical trials of adjuvant early generation EGFR-TKIs suggest poor disease control due to poor blood-brain barrier penetration.[17-19] Unlike earlier generation EGFR-TKIs, osimertinib is a highly selective therapy capable of crossing the blood-brain barrier to prevent CNS metastases.[23,24] The reduction in CNS metastases with adjuvant osimertinib is expected to provide an OS benefit. [redacted]

Key issue	Does this response contain new evidence, data or analyses?	Response
		3: Osimertinib has already demonstrated significant OS benefit in NSCLC The metastatic setting is generally considered by clinicians as more difficult to treat and patients typically progress faster. Despite this, osimertinib has already demonstrated a superior OS benefit versus first-generation TKIs supported by a significant and sustained extension in PFS and a significant reduction in the risk of CNS metastases. In FLAURA, which evaluated osimertinib for the first-line treatment of metastatic EGFRm NSCLC, osimertinib was associated with a significant reduction in the risk of CNS progression by 52% vs comparator EGFR-TKIs (HR 0.48; p=0.014). Osimertinib was also the only first-line treatment with median overall survival beyond 3 years (HR 0.80; p=0.046). Osimertinib was also associated with clinically meaningful benefits in median PFS in patients with CNS metastases (8.5 months for osimertinib vs 4.2 months for platinum-based chemotherapy (HR 0.32)). **Osimertinib as an adjuvant treatment will result in cancer-free years to patients by significantly extending DFS. Due to the unprecedented magnitude of the DFS benefit, the significant reduction in CNS metastases and the consistent OS benefit observed in the metastatic setting, osimertinib is expected to result in significant improvements to long-term survival in the adjuvant setting.**
Key issue 2: Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib	**NO**	**Osimertinib represents the mainstay treatment option and is considered the current standard of care in 1L locally advanced/metastatic EGFRm NSCLC.** Updated national prescribing data provided in the factual accuracy form following the ERG Report confirm that osimertinib is the mainstay treatment option in first-line locally advanced/ metastatic EGFRm NSCLC. National audit data demonstrates the usage of osimertinib has been rapidly increasing. Following receipt of the updated prescribing data, the ERG updated Additional Sensitivity Analysis 3 to reflect the latest market shares for TKIs in first-line metastatic disease. As osimertinib was recently recommended by NICE for first-line treatment of metastatic disease (NICE TA654,

Key issue	Does this response contain new evidence, data or analyses?	Response
		October 2020), it is expected that its use will continue to increase as more newly diagnosed patients with metastatic disease are treated with osimertinib. The Company acknowledge that the availability of adjuvant osimertinib may lead to changes in clinical practice in the future. However, the impact of adjuvant osimertinib on the clinical treatment pathway is currently unknown and cannot be accurately predicted. Furthermore, NICE decisions are made on a national basis and should reflect current NHS clinical practice.
Key issue 3: Uncertainty surrounding company's cure assumptions and OS predictions	**YES**	**Real-world evidence validates curative potential of treatment for resected EGFRm NSCLC** As discussed in the Company Submission (Section B.3.3.3.1), published clinical trial evidence in resected NSCLC demonstrated a plateauing effect in DFS rates at approximately 48-60 months following surgical resection, indicating that 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. [redacted]

		Figure 2: Real-world DFS Kaplan-Meier curve  **The assumption of cure at 8 years for the osimertinib arm is excessively pessimistic** The assumption of a 5-year cure in both arms is supported by published clinical evidence and expert clinical opinion (CS, Section B.3.3.3). Clinical trial data in stage IB–IIIA, completely-resected NSCLC indicates that at around 48–60 months, a proportion of patients are no longer at risk of disease recurrence. UK clinicians agreed that patients who are disease-free at 5 years would have a very low risk of recurrence, their survival would be similar to that of the general population and these patients are considered functionally cured.

Key issue	Does this response contain new evidence, data or analyses?	Response
		The ERG's assumption of an 8-year cure for osimertinib is likely to be overly pessimistic. However, a 6-year cure timepoint for osimertinib would reflect an appropriate alternative pessimistic scenario that is supported by UK clinical opinion. Clinicians interviewed by the Company advised that the majority of patients progress within 18-24 months post-resection (CS, Section 1.3.2, Page 20). Following the assumption that adjuvant osimertinib delays some recurrences rather than preventing, we can assume that the cure timepoint would be at 6 years. This takes into account the total duration of treatment (3 years), followed by an additional period to account for delayed disease recurrence (2 years), with an extra year added to remain conservative. In light of this, we have provided results for the ERG's preferred and exploratory analyses in the updated pessimistic scenario (Appendix A). **ERG ASA5 provides clinically implausible and pessimistic estimates of adjuvant osimertinib long-term survival that contradict clinical data and opinion** This sensitivity analysis assumes that the cumulative hazards for adjuvant osimertinib and placebo will be approximately equal at the respective cure timepoints in the pessimistic scenario (8 years for osimertinib, 5 years for active monitoring). The distributions for osimertinib for TP1 and TP2 are selected so that the survival probability at 8 years in the osimertinib arm is equal to the survival probability at 5 years in the active monitoring arm. By setting the survival probabilities for adjuvant osimertinib and active monitoring to be equal at their relative cure timepoints suggests that adjuvant osimertinib is not associated with a long-term DFS benefit which contradicts clinical evidence from the ADAURA trial and clinical expert opinion.

Figure 3: Aggregated DFS – ERG's preferred pessimistic analysis

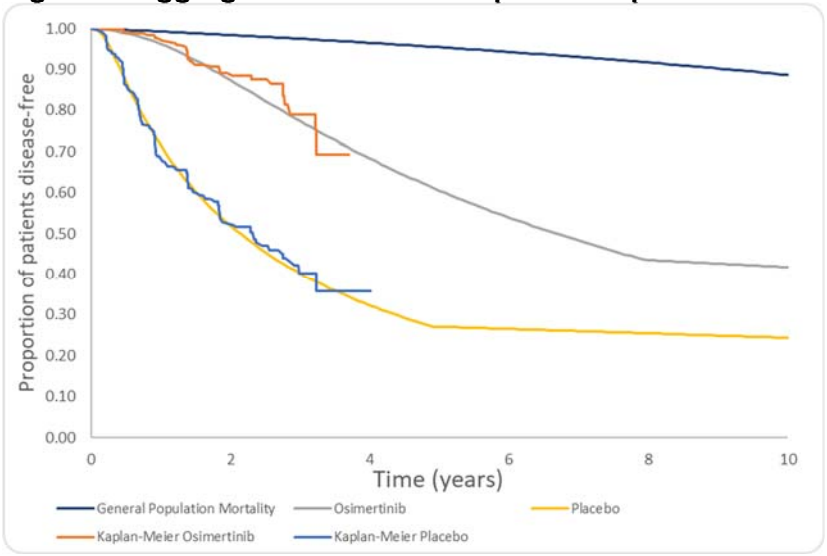
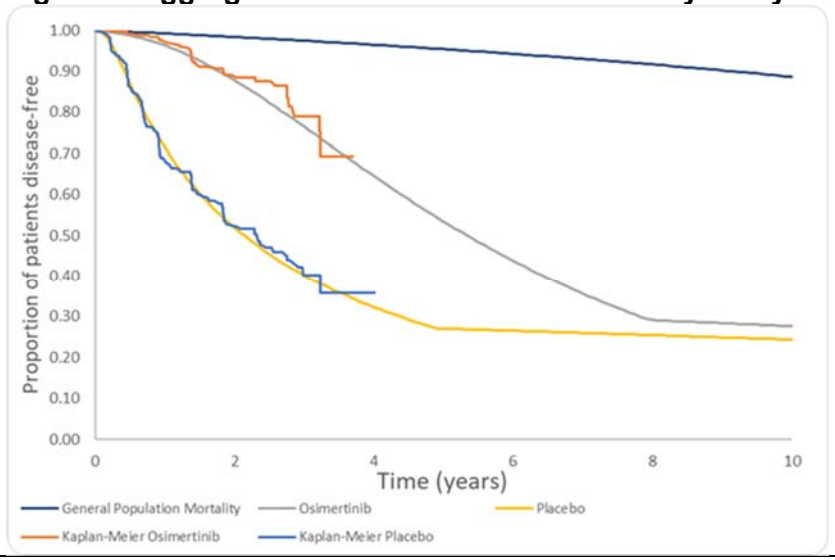


Figure 4: Aggregated DFS – Additional Sensitivity Analysis 5



Key issue	Does this response contain new evidence, data or analyses?	Response
		As shown in Figure 3 and Figure 4, this additional sensitivity analysis has two key ramifications: 1. The proportion of patients disease-free in the osimertinib arm at 8 years (and therefore eligible to be 'cured') is reduced from [redacted] 2. There is no further significant DFS benefit associated with adjuvant osimertinib after 8 years When compared to clinical trials and real-world studies in this population, it is apparent that the DFS estimates included in this sensitivity analysis for osimertinib are excessively pessimistic. The proportion of patients disease-free at 8 years in this additional sensitivity analysis (ASA) for osimertinib is similar to DFS rate in the observation arm of the ANITA study (30.5%)[25]. Patients in the observation arm in the ANITA trial did not receive active treatment. Furthermore, patients receiving observation in ANITA had a poorer prognosis compared to osimertinib-treated patients in ADAURA, due to the inclusion of squamous cell carcinomas (58% in ANITA observation arm; ADAURA excluded squamous NSCLC), a greater proportion of male patients (87% versus 32%) and a smaller proportion of patients with a performance status of 0 (52% versus 64%). Given the significant differences in patient populations and the unprecedented DFS improvement with adjuvant osimertinib compared to placebo in ADAURA, it is excessively pessimistic to assume osimertinib will result in similar long-term DFS rates to patients who receive no adjuvant treatment. Furthermore, UK clinicians consulted through an advisory board and 1:1 interviews stated that the DFS benefit observed with osimertinib at interim data cut is expected to translate into a long-term survival benefit. This prediction is based on the unprecedented DFS benefit observed with osimertinib in ADAURA, the reduced rate of recurrence of distant/CNS metastases observed with osimertinib versus placebo, and the benefits in OS and CNS recurrence with osimertinib vs first- and second-generation EGFR-TKIs in the metastatic NSCLC setting demonstrated in FLAURA. Additionally, the Company conducted a restricted mean survival time (RMST) analysis using the area under the ADAURA DFS KM curves for the overall population. The analysis estimated an RMST of [redacted] months for adjuvant osimertinib and [redacted] months for placebo, resulting in a difference of [redacted] months based on observed data from the trial. In contrast, ERG ASA5 results in an estimated

Key issue	Does this response contain new evidence, data or analyses?	Response
		mean OS gain of 1.32 years (15.84 months); suggesting a residual post-recurrence benefit of just ~ 4 months associated with adjuvant osimertinib. This undermines the numerical overall survival benefit already observed with adjuvant osimertinib and provides further support against the clinical plausibility of ASA5.
Key issue 4: Uncertainty regarding re-treatment with osimertinib	**NO**	**Re-treatment with osimertinib is supported by UK clinical opinion** The Company acknowledge that osimertinib as an adjuvant treatment for fully-resected EGFRm-positive NSCLC is an innovative step-change in the treatment pathway and therefore the impact on the downstream treatment pathway of introducing osimertinib in the adjuvant setting is not fully known. Nonetheless, UK clinicians consulted in interviews agreed that they would consider retreatment with osimertinib for patients who successfully completed 3 years of adjuvant treatment with osimertinib and who did not relapse within a year of treatment completion. Clinical experts advised that retreatment with other EGFR-TKIs would not be considered as these are less potent and less efficacious than osimertinib. Clinical advisors to the ERG also indicated that re-treatment may be appropriate for patients whose disease did not recur whilst receiving adjuvant osimertinib or within a short time of completing adjuvant treatment (Section 1.5, Page 17). The Company is aware that personal communication from NHS England has advised that re-treatment with osimertinib would not be permitted. However, the Company has not been advised directly by NHS England of this position, nor are aware of the clinical justification for this restriction to be imposed. TKI therapies, and in particular, osimertinib, represents the mainstay treatment option for the first-line treatment of patients with EGFRm positive mNSCLC. This practice change is underpinned by the superior efficacy and tolerability of targeted oral TKI therapy compared with platinum-doublet chemotherapy. It would be reasonable to conclude that the adjuvant treatment with osimertinib in patients following complete resection was successful if a patient successfully completes 3-years of treatment without the need to discontinue due to unacceptable toxicity or disease recurrence. In these patients, it is reasonable to conclude that osimertinib treatment is effective, and they are unlikely to have developed any treatment resistance mechanisms. Therefore, in the event that these patients later experience disease recurrence, there is no clinical rationale for restricting their access to highly-effective, well-tolerated TKI therapies, resulting in their only option to

Key issue	Does this response contain new evidence, data or analyses?	Response
		receive treatment with PDC. Clinicians have unanimously supported the need to consider TKI re-treatment in those patients that have successfully received earlier adjuvant TKI therapy. Therefore, we urge NICE and NHS England to reconsider their position in light of the evidence and clinical need to enable optimal treatment of patients with first-line EGFRm positive mNSCLC.
Key issue 5: Limitations of available utility values for EGFRm-positive NSCLC	**NO**	**There is a significant lack of published utility values for resected EGFRm NSCLC** The Company acknowledge the limitations with the assumptions regarding health-state utility values applied in the economic model. In response to ERG clarification questions, the Company updated the utility value for DFS (and therefore LRR) to be equal to general population estimates. The Company also agree with the ERG's clinical advisors that patients with locoregional recurrence will likely not have the same level of quality of life as those who are disease-free in clinical practice, due to the cumulative impact of treatments received (surgery, radiotherapy and/or chemotherapy). However due to the lack of QoL data in patients with LRR in the ADAURA trial and the lack of estimates in the literature, this simplifying assumption was necessary. It is important to acknowledge that applying the same value in the LRR state as DF favours the active monitoring group in the economic analysis. There is a significant lack of published available utility values for EGFRm NSCLC, particularly in the earlier disease stages. This was also noted on Page 18 of the ERG report; "The ERG is unaware of any alternative relevant sources which could be used to inform the health utility values in the model."
Key issue 6: Absence of subgroup analyses for patients with stage IB NSCLC	**NO**	**There is a great unmet need in stage IB disease for effective, targeted adjuvant treatments** Despite a perceived lower unmet need in stage IB disease, disease recurrence rates remain unacceptably high, with studies showing that 45% of patients with stage IB NSCLC recur within 5 years following surgery.[10] In addition, a pooled analysis from five 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 57% of patients diagnosed with stage I NSCLC will survive for at least 5 years. As such, there is a significant need to improve the outcomes for patients with stage IB NSCLC.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Osimertinib has demonstrated a significant DFS benefit in stage IB Osimertinib as an adjuvant treatment in ADAURA 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 61% reduction in the risk of disease recurrence or death in stage IB patients (HR: 0.39; 95% CI: 0.18, 0.76) compared with placebo, further supporting the significance of the benefit across all patients enrolled in the study. This clear and significant improvement in DFS was maintained without impacting quality of life, with no clinically meaningful differences in health-related quality of life compared to placebo. **Osimertinib as adjuvant treatment for stage IB will be a cost-effective use of NHS resources** Due to the reduced risk of recurrence in patients with stage IB disease vs those with more advanced disease and the unblinding of the study two years early due to overwhelming efficacy, the data in patients with stage IB disease are highly immature, with just [redacted] events reported in patients receiving osimertinib vs placebo, respectively, at the time of data cut-off. Furthermore, the study was not powered to assess the efficacy in patients by stage of disease. Due to these significant limitations, it was deemed inappropriate to assess the cost-effectiveness of osimertinib in patients with stage IB disease alone. However, as the study was powered to evaluate the efficacy of patients in the primary population (i.e. patients with stage II−IIIA disease) and overall population (i.e. patients with stage IB−IIIA disease), the Company provided a scenario analysis to demonstrate the cost-effectiveness of osimertinib in the primary population i.e. in those with stage II−IIIA disease alone. This analysis excludes patients diagnosed with stage IB disease and therefore enables the relative cost-effectiveness to be evaluated when patients with stage IB disease are either included or excluded in the analysis. The base case ICER for the primary population was £5,292. Since the base case analysis ICER has remained well below the cost-effective threshold when considering the overall population (stage IB-IIIA: £9,979) and when considering the primary study

Key issue	Does this response contain new evidence, data or analyses?	Response
		population (stage II-IIIA: £5,292), we can therefore expect that stage IB will represent a cost-effective use of NHS resources. **AstraZeneca believes it is inappropriate to consider an analysis by subgroup** The Company would like to highlight the recent appeal for TA504 in which the consideration of subgroups was challenged by the appellant.[26] The conclusions of the appeals highlighted that:[26] • Unless a scope specifies otherwise, the Appeal Panel considers that there is a soft presumption that the starting point for any Committee should be consideration of the whole patient group as one, with a view to making one recommendation for that group. Where different recommendations are to be made for different groups of patients, the reason for departing from one recommendation should be clear and adequate, and • As far as the reasonableness of considering subgroups is concerned, the Panel tended to agree with Meindert Boysen that in a case where it appeared that use of a product was acceptably cost effective in a whole population, it would not normally be reasonable to look for subgroups within that population where use was cost ineffective. However, it would go too far to make that a general rule. Hypothetically if a committee was aware that there existed an identifiable subgroup defined for a proper purpose and in a logical way and in which use was clearly not cost effective, then it might be difficult to say that taking account of that subgroup was unreasonable. The final scope for this appraisal states: "*If the evidence allows, subgroups based on NSCLC stage (Ib versus II-IIIa) may be considered".*[27] As outlined above, the data in patients with stage IB disease are highly immature, with just [redacted] events reported in patients receiving osimertinib vs placebo, respectively, at the time of data cut-off. In addition, the study was not powered to assess the efficacy in patients by stage of disease and therefore it was deemed inappropriate to assess the cost-effectiveness of osimertinib in patients with stage IB disease alone. As an alternative scenario, the Company provided a scenario analysis to demonstrate the cost-effectiveness of osimertinib in the primary population i.e. in those with stage II−IIIA disease alone, thereby excluding patients with stage IB disease. Both the base case and the alternative scenario result in ICERs significantly below the

Key issue	Does this response contain new evidence, data or analyses?	Response
		cost-effective threshold, and osimertinib can be considered a cost-effective use of NHS resources, irrespective of stage of disease. Given this, and the data immaturity of the stage IB population, the Company firmly believes that there is no reason to conclude that there is a population in which treatment is clearly not cost effective, and there is no clearly identifiable subgroup or logical reason for undertaking such an analysis.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	**YES/NO**	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key Issue 1 (Section 5.3.4 in ERG Report)	The Company submission included a 5-year cure assumption applied to both arms, supported by published clinical evidence and expert clinical opinion. The ERG's preferred pessimistic analysis, which assumes an 8-year cure for osimertinib, is overly pessimistic. However, a 6-year cure timepoint for osimertinib would reflect an appropriate alternative pessimistic scenario that is supported by UK clinical opinion. In light of this, we have provided results for the ERG's preferred and exploratory analyses in the updated pessimistic scenario (Appendix A).	The ERG's assumption of an 8-year cure for osimertinib in is likely to be overly pessimistic. However, a 6-year cure timepoint for osimertinib would reflect an appropriate alternative pessimistic scenario that is supported by UK clinical opinion. In light of this, we have provided results for the ERG's preferred and exploratory analyses in the updated pessimistic scenario (Appendix A).	Company's preferred pessimistic analysis: £13,361 ERG's preferred pessimistic analysis: £20,417 Change in ICER: £7,056

Appendix A: Company's revised "ERG report Table 49"

Additional sensitivity analysis	Optimistic scenario - cure point at 5 years			Pessimistic scenario - cure point at 6 years for osimertinib[1], placebo at 5 years		
	Inc. QALYs	Inc. costs	ICER	Inc. QALYs	Inc. costs	ICER
ERG preferred analysis	[redacted]	[redacted]	**£9,979**	[redacted]	[redacted]	**£13,361**
ASA1: Use of utilities from Andreas	[redacted]	[redacted]	**£10,467**	[redacted]	[redacted]	**£13,927**
ASA2: Assume AE QALY loss for one year for adjuvant osimertinib	[redacted]	[redacted]	**£9,988**	[redacted]	[redacted]	**£13,374**
ASA3a: Different mix of TKIs (updated data)	[redacted]	[redacted]	**£19,391**	[redacted]	[redacted]	**£23,996**
ASA4a: Use log-normal for TP2 (DF to DM1) in both arms	[redacted]	[redacted]	**£9,334**	[redacted]	[redacted]	**£13,837**
ASA4b: Use log-normal for TP2 (DF to DM1) in treatment arm only	Not clinically plausible					
ASA5: Use log-logistic for TP1 (DF to LR) and log-normal for TP2 (DF to DM1), treatment arm only	Not clinically plausible					
ASA6: Halve EGFR testing cost to account for some tests already	[redacted]	[redacted]	**£9,818**	[redacted]	[redacted]	**£13,177**
ASA7: Allow re-treatment with osimertinib	[redacted]	[redacted]	**£10,808**	[redacted]	[redacted]	**£14,837**
ASA8: Alternative proportion of patients receiving whole-brain radiotherapy for CNS metastases	[redacted]	[redacted]	**£9,857**	[redacted]	[redacted]	**£13,234**

Abbreviations: QALY, quality-adjusted life year; ICER , incremental cost,-effectiveness ratio; Inc. , incremental; ASA , additional sensitivity analysis; DF – disease-free; LRR , locoregional recurrence; DM1, first-line distant metastasis; CNS , central nervous system; TKI , tyrosine kinase inhibitor; EGFR , epidermal growth factor receptor

[1] This pessimistic scenario takes into account the total duration of treatment with adjuvant osimertinib (3 years), the period of time at which patients are at the greatest risk of recurrence (2 years), to account for potential delayed recurrence and an additional year to remain conservative.

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Clinical expert statement & technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 20 May 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection and current treatment options	
About you	
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 non-small-cell lung cancer after complete tumour resection? ☐ a specialist in the clinical evidence base for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection or technology? ☐ 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	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent lung cancer progression and death after successful lung cancer surgery.
9. What do you consider a clinically significant treatment	More than 50% reduction in recurrent cancer and / or death.

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR mutation-positive non-small-cell lung cancer after complete tumour resection?	Yes, no specific targeted treatment are available for patients who are EGFR mutation positive. Eligible patients are offered adjuvant chemotherapy (of which only 50% accept due to concerns about the side effects from general chemotherapy).
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Patients with EGFR mutation after complete surgery (with lymph node disease) are offered general chemotherapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are no current guidelines for completely resected EGFR mutant lung cancer.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Pathway is well defined in the sense that there is no other option available.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would require surgeons to screen node positive patients whom underwent complete resection for EGFR mutations.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Where reflex genomic testing is being undertaken, screening will be considered standard care. Currently osimertinib is used only in the advanced setting.
• How does healthcare resource use differ between the technology and current care?	The addition of osimertinib to selected patients after complete lung cancer resection for three years.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	I believe NICE should consider investing in training and supporting surgeons who have an interest in surgical oncology to prescribe osimertinib and continue longer term care for their patients.
13. Do you expect the technology to provide clinically meaningful	Yes

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	The data is not out yet, but yes, I expect it will prolong life.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, improvement in HRQoL by avoiding the pain, complications and costs of treating recurrent and progressive cancer for three years.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes, EFGR mutation positive patients.
The use of the technology	
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	Slightly more difficult in the sense that screening is required, follow up arrangements will be needed to take into account for screening of complications from treatment (although in general the drug is very well tolerated).

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Progression of disease as a stopping rule, which is something that we already undertake by chest x ray and CT.
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?	Yes, mental wellbeing, and the ability to stay out of hospitals to allow patients with cancer to live their lives with their loved one and family – to many that is what quality of life means.
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	Yes, with an unpresented amount of reduction in recurrence of cancer.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes, nothing apart from generalised chemotherapy is offered at present.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, target specific treatment.
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?	In general the side effect profile is very good with mild diarrhoea as the most common side effect.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes is does.
• 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?	Disease free survival - yes it was measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware.
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?	In UK, frequency of EGFR mutation positive patients after lung cancer resection is likely to be much lower (<5%) than the ADAURA cohort.
Equality	

23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes, EGFR mutation positive tend to occur more in women and BAME (Chinese).
23b. Consider whether these issues are different from issues with current care and why.	Not that I am aware.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS – Is disease free survival an appropriate surrogate for overall survival?	It measures more than a binary dead or alive, and I believe is more reflective of the burden of the disease when one is alive.
Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib – What impact would the technology have on the current pathway of care?	If patients were to progress on osimertinib, then the appropriate second or third line agents will be prescribed. The benefit of osimertinib is to prevent or delay progression of disease.

Uncertainty surrounding the company's cure assumptions and OS predictions	It is not fault of the company if the DSMC has stopped the trial early for overwhelming benefit, one also needs to take into account the welfare of the participants in ADAURA.
Uncertainty regarding re-treatment with osimertinib – Is it appropriate to assume that some people will get osimertinib in the metastatic setting after having received adjuvant osimertinib?	Ideally osimertinib should be given continuously, so this won't be an issue. Stopping it at an artificial time point of three years predisposes to rebound cancer.
Limitations of available utility values for EGFRm-positive NSCLC	
Absence of subgroup analyses for patients with stage IB NSCLC – Is Osimertinib more or less effective in people with stage IB disease compared with the whole population?	There was no evidence of an interaction effect.

PART 3 -Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is no targeted option for patients with EGFR mutant lung cancer completely resected by surgery
- Osimertinib provides unprecedented reduction in prevention of recurrent cancer and allows patients to live their lives with their families
- Osimertinib may improve overall survival
- Surgeons are best placed to administer osimertinib (if licenced) to improve continuity of care of the patient after surgery as part of follow up and screening for recurrent disease

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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Clinical expert statement & technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

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- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 20 May 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection and current treatment options	
About you	
1. Your name	**Dr Gary Doherty**
2. Name of organisation	**Cambridge University Hospitals NHS Foundation Trust**
3. Job title or position	**Consultant Medical 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 non-small-cell lung cancer after complete tumour resection? ☒ a specialist in the clinical evidence base for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection or technology? ☐ 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	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None.**
The aim of treatment for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to delay or prevent disease recurrence after cancer resection, and (as a result) delay or prevent symptoms and complications of disease recurrence. Disease recurrence results in significant patient morbidity and mortality, including (but not limited to) the preponderance of intracranial metastases that occur in patients with EGFR mutation-positive NSCLC.

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.)	This is a disease of significant unmet need, with no treatment options available after chemotherapy to delay or prevent disease recurrence (and progression to the incurable state). As a result the bar for a clinically significant treatment response is low. I would consider the following to be clinically significant for this patient group: a >/= 5% improvement in the probability of disease-free survival AND/OR a >/=10% improvement in the cumulative incidence of intracranial disease-free survival AND/OR a significant improvement in health-related quality of life AND/OR any improvement in patient overall survival.
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR mutation-positive non-small-cell lung cancer after complete tumour resection?	Yes. These patients have a high probability of disease relapse to the incurable state, despite optimal current management and suffer significant morbidity and mortality as a result.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	After tumour resection (preceded by optimal pre-surgical staging) and assessment by a specialist histopathologist and a lung cancer MDT, patients with EGFR mutant NSCLC are currently “offered” four cycles of cisplatin-based combination chemotherapy if they have N1+ disease, and this is “considered” for N0 patients with primary tumour size greater than 4cm in diameter (as per NICE guidelines [NG122]). Patients then enter protocolised follow up for surveillance to detect relapse.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guideline [NG122] – Lung Cancer: Diagnosis and Management; published 28 March, 2019.

• 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.)	While NG122 is clear about which patients should be offered/considered for adjuvant chemotherapy, there is heterogeneity in use of adjuvant chemotherapy in the UK. The optimal follow up protocol (how often, which assessments, by whom etc.) for these patients after surgery +/- adjuvant chemotherapy is less defined, with NG122 (last reviewed in 2011) not commenting on which protocol(s) should be used – this results in significant geographical and inter-clinician variability with regard to local follow up schedules and assessments, which may vary by disease stage +/or likelihood of disease recurrence.
• What impact would the technology have on the current pathway of care?	There will be impact on pathology services (referral for somatic genomic testing for EGFR alterations) and NHS Genomic Laboratory Hub services, in order to identify EGFR mutant cases of resected NSCLC – there is heterogeneity across the country with regard to the stages of disease that trigger EGFR genomic testing and the technology will result in an increased need for equitable testing in patients with early stage disease. All patient cases will be discussed in lung cancer MDTs (as before), although this may result in some additional workload for lung cancer MDTs. Patients with EGFR mutation-positive cases will then be referred to oncology specialist services for discussion of adjuvant treatment (to discuss chemotherapy and adjuvant osimertinib) – the impact of the technology at this stage will be minimal. Should patients commence adjuvant osimertinib, their care will be with specialist oncology services (impacting medical/clinical oncology clinicians, clinical nurse specialists and outpatient oncology pharmacy services) for at least the duration of osimertinib treatment, which is a change in the usual pathways of care (with most patients otherwise being followed up by thoracic services). Overall, the impact will be limited and proportionate.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No, with the exception that at the time of writing, an agreement with NICE/NHSE/AstraZeneca has been made to provide Osimertinib for this indication. Relevant services are now adapting to the availability of osimertinib in this setting.
• How does healthcare resource use differ between	Standard care currently is protocolised follow up (see above) with periodic clinical and radiological review, with no further systemic anti-cancer treatment after surgery +/- adjuvant chemotherapy. The technology will require increased regular clinic appointments (with most of these likely to be virtual in future), blood tests and ECGs for

the technology and current care?	safety monitoring, increased oncologist and specialist nursing resource use, increased outpatient oncology pharmacy resource use, and (likely) increased radiology resource use. There will likely be reduced healthcare resource use on other services, including acute oncology services, emergency services, radiotherapy services and other services that manage complications of cancer progression.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist lung oncology clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Since oncology and pharmacy services are routinely using osimertinib in the metastatic disease setting, limited investment will be required, although education will be needed to optimise clinical pathways. There will be cost implications for pathology and genomic testing services, but this is part of the NHS Genomic Medicine Service for Cancer and is part of an ongoing and broader national project.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. The results from the phase III ADAURA trial detail the highly significant and clinically meaningful improvement in patient-relevant outcomes, which represent a very significant step-wise improvement in the optimal care of these patients.
• Do you expect the technology to increase length of life more than current care?	Yes. To me it seems biologically and clinically implausible that such a large benefit in improving disease-free survival will not translate into a significant and clinically meaningful improvement in overall survival for these patients, and this appears to be being borne out by the immature overall survival analyses presented to date.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. There may be a reduction in real world HRQOL over the short term given potential toxicities from the technology, but over the long term (particularly given the technology's good safety profile), delays or prevention of recurrence (which are associated with significant reductions in real world HRQOL) will likely favour the technology improving real world HRQOL overall.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not currently known. The Forest plot for DFS at interim analysis per subgroup does not suggest any relevant significant additional or lower benefit for any subgroup. The hazard ratio for DFS in Stage IB patients suggests less improvement for this group, compared with Stage II-IIIA patients, but this remains highly clinically significant for Stage IB patients, who (despite being at lower risk of recurrence than Stage II-IIIA patients) still have a high recurrence risk (see later). The same is true for patients with L858R mutations who also have clearly significant benefit.
The use of the technology	
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.)	The use of the technology closely mirrors the use of Osimertinib in the locally advanced/metastatic disease setting, and as such there will be little impact of the technology (aside from an increased number of patients on treatment) compared with currently offered care in the locally advanced/metastatic disease setting. Practical implications for its use will mirror this setting and as per the SmPC (awaited for this indication at the time of writing) – additional requirements (in additional to clinician input) will include ECGs and safety blood tests.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	Starting and stopping rules will likely to reflect the eligibility criteria for the ADAURA trial and treatment will likely continue until unacceptable toxicity, disease relapse, or should the patient wish to discontinue treatment. Additional testing has been covered in preceding sections.

Do these include any 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?	Not definitively, although I do not see psychological aspects included – I expect mental health to be improved for patients with the technology versus active surveillance; this could be discussed with the expert patient representatives.
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?	Yes, the technology is a highly effective, highly targeted drug that targets cancer cells harbouring very specific EGFR genomic alterations, with low toxicity. It very significantly reduces the risk of disease relapse. As such it represents an innovative method to produce a step change in clinically meaningful patient outcomes, with clear improvements in meeting the significant unmet needs in the patient population being considered.
• Is the technology a 'step-change' in the management of the condition?	Yes, undoubtedly so.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, detailed in preceding sections.

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?	In the real world, osimertinib is a well-tolerated drug in the locally advanced/metastatic disease setting, and this is backed up by the ADAURA trial data in the adjuvant setting. While osimertinib is associated with toxicity, these are modest and the relevant clinical teams are experienced in managing these toxicities and maintaining quality of life while on treatment.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the comparator (placebo) arm in the ADAURA trial closely reflects active surveillance for relapse that occurs in standard UK clinical practice, with the exception that the patients included in the trial are likely to have had closer surveillance for detection of relapse than in standard clinical practice (which may lead to improved outcomes in the placebo arm versus real world patients in the UK). The use of adjuvant chemotherapy in the ADAURA trial was similar to that in standard UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Disease-free survival – measured in the ADAURA trial. Intracranial disease-free survival – measured in the ADAURA trial. Overall survival - measured in the ADAURA trial (results immature and will be affected by decision to unblind). Health-related quality of life - measured in the ADAURA trial.

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Disease-free survival, in my opinion, is an appropriate primary endpoint for this study. The precise extent of overall survival benefit remains uncertain and will likely be affected significantly by the decision to unblind the trial. However, the definition of long term is relative and subjective: for these patients already at high risk of relapse who are receiving up to three years of osimertinib treatment with a median follow up for the primary endpoint of 22.1 months in the osimertinib arm, I see this already being long term from my clinical perspective.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No, none to my knowledge.
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?	None available as yet in this specific patient population, but extrapolation from the locally advanced/metastatic setting suggests that real world and trial experiences will be similar.
Equality	
23a. Are there any potential equality issues that should be	There is a higher proportion of EGFR mutation-positive NSCLC (as a proportion of the total population with NSCLC) in Asian patients, and this technology may therefore help improve health outcomes in Asian patients.

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	N/A

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS – Is disease free survival an appropriate surrogate for overall survival?	Yes. And discussed above. DFS in itself is a clinically significant and meaningful endpoint. I find it biologically and clinically implausible, with my knowledge of the natural history of this disease as well as the hazard ratios presented and the early immature overall survival data reported, that this magnitude of benefit will not translate into a clinically meaningful and significant overall survival benefit (albeit this will be likely confounded by early unblinding in the ADAURA trial follow up data). Often these patients relapse in manners that (a) preclude further treatment (e.g. death/significant morbidity); (b) preclude optimal treatment (e.g. deterioration in performance status such that treatment with osimertinib in the relapsed setting is not possible under current commissioning criteria; and (c) result in poorer prognosis (e.g. development of CNS metastases).
Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib – What impact would the technology have on the current pathway of care?	This will depend on treatments available at relapse for patients, which will likely change over time based on the prevailing evidence. For patients who progress *during* treatment with osimertinib, they have had/developed osimertinib-resistant disease, and treatment will be dictated by available therapies, the patient's ECOG performance status (and other patient factors) and the availability of clinical trials. At the moment in standard care, these patients are likely to be treated with chemotherapy alone or the combination of atezolizumab, bevacizumab, carboplatin and paclitaxel. For patients who progress *after* treatment with osimertinib, in my opinion they should be treated as per other patients presenting *de novo* with metastatic disease and would best be treated with osimertinib if they meet

	prevailing treatment criteria for this setting – patients who relapse *after* osimertinib by definition did not have curable disease and (given the duration of adjuvant therapy) osimertinib will be very likely to have been controlling micrometastatic disease. After removal of this drug (and therefore the effect of controlling this metastatic disease) tumour relapse will become clinically apparent in this population after a period of time, but the relevant tumour cell population will still harbour the driving EGFR mutation, growing as a result of the removal of the treatment selection pressure. In my opinion, it would be unethical not to offer rechallenge of osimertinib to these patients, although the extent of benefit may differ from that reported in the FLAURA trial (or may not).
Uncertainty surrounding the company's cure assumptions and OS predictions	The real world clinical outcomes for patients with resected EGFR mutation-positive NSCLC are unclear, but this is a subset of NSCLC with a high propensity for early metastatic spread, as demonstrated by the DFS data in the placebo arm of the ADAURA trial. In my personal opinion from the clinical perspective, these patients have shorter DFS than the general NSCLC population and are less likely to be cured by surgery +/- adjuvant chemotherapy than the general NSCLC. When these patients relapse clinically, this is often accompanied by relapse-related morbidity/mortality and an inability to offer the best standard of care treatment (osimertinib) as a result – this leads me to believe that the placebo group in the setting of the ADAURA trial (with more careful follow up for recurrence than is likely to be achieved in standard care) will have longer overall survival than those on active surveillance for relapse in the real world (likely to present later than in the ADAURA population). These, and other factors, lead me to believe that the company's OS predictions (and the ERG model) are conservative with regard to the benefit of adjuvant osimertinib – I believe the magnitude of benefit will be greater in the real world for patients than that presented.
Uncertainty regarding re-treatment with osimertinib – Is it appropriate to assume that some people will get osimertinib in the metastatic setting after having received adjuvant osimertinib?	Yes. I have detailed this above in response to the second question in this section.

Limitations of available utility values for EGFRm-positive NSCLC	We have limited data in the EGFR-mutation positive patient population and have little to add to the expert opinion in the ERG group – the truth is likely to lie somewhere in between both approaches. This is all highly speculative.
Absence of subgroup analyses for patients with stage IB NSCLC – Is Osimertinib more or less effective in people with stage IB disease compared with the whole population?	Osimertinib appears highly effective in the Stage IB subgroup of the ADAURA trial in improving disease-free survival, again with an impressive hazard ratio, albeit lower than that in the Stage II-IIIA subgroup. I do not feel it is fair to judge these groups differently and this was not the trial design – with regards to the Stage IB group, the comparison should simply be between the effectiveness of osimertinib versus placebo in this group, not if it is more or less effective than in a different patient population. The main take home message here for me is the surprisingly high risk of relapse in this early stage group, and how effective osimertinib is in reducing this risk.

PART 3 -Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Osimertinib is highly effective in prolonging disease-free survival in patients with Stage IB-IIIA, resected, EGFR mutation-positive non-small cell lung cancer
- Osimertinib is well tolerated by patients with resected EGFR mutation-positive non-small cell lung cancer in the adjuvant setting
- Osimertinib results in positive health outcomes that are clinically meaningful for this patient group
- Osimertinib availability for this patient population will necessitate reflex testing for EGFR genomic alterations in Stage IB-IIIA resected non-small cell lung cancer
- Adjuvant osimertinib is the most significant advance to date for this population of patients with significant unmet need

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 20 May 2021**.

Completing this form

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Important information on completing this expert statement

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PART 1 – Treating a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection and current treatment options	
About you	
1. Your name	**Andrew Robinson**
2. Name of organisation	**Royal College of Pathologists**
3. Job title or position	**Consultant Histopathologist**
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 non-small-cell lung cancer after complete tumour resection? ☐ a specialist in the clinical evidence base for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection or technology? ☐ 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	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	
9. What do you consider a clinically significant treatment	

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in EGFR mutation-positive non-small-cell lung cancer after complete tumour resection?	
What is the expected place of the technology in current practice?	
11. How is the condition 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?	
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 clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	EGFR testing for NSCLC is common practise now within pathology departments however there is variation in how and when this is performed. Some centres perform reflex testing on all NSLCL irrespective of subtype and staging whilst others may only perform EGFR testing when requested by oncologists and limit EGFR testing to adenocarcinomas. This new technology may result in an increased demand to test NSCLC tumours for EGFR mutations (in particular Stage IB resections which may not have been previously tested in some centres in the past) and this increased cost needs to be considered in the economic model. These costs have already been recognised and addressed by the ERG in their analysis.

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?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
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.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any 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?	
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?	
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?	
Sources of evidence	
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?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS – Is disease free survival an appropriate surrogate for overall survival?	
Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib – What impact would the technology have on the current pathway of care?	

Uncertainty surrounding the company's cure assumptions and OS predictions	
Uncertainty regarding re-treatment with osimertinib – Is it appropriate to assume that some people will get osimertinib in the metastatic setting after having received adjuvant osimertinib?	
Limitations of available utility values for EGFRm-positive NSCLC	
Absence of subgroup analyses for patients with stage IB NSCLC – Is Osimertinib more or less effective in people with stage IB disease compared with the whole population?	

PART 3 -Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Increased demand and costs for EGFRm testing needs to be appropriately factored into the economic model and this has already been addressed by the ERG review.
- The technical engagement questions highlighted above are best answered by the oncology and surgery clinical experts.
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Thursday 20 May 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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. The text boxes will expand as you type.

Important information on completing this expert statement

- 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection and current treatment options	
About you	
1.Your name	**Jenny Abbott**
2. Are you (please tick all that apply):	☐ a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection? X☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	EGFR Positive UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) X☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement X☐ Yes, I authored / was a contributor to my nominating organisations submission X☐ 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/experience (e.g. 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
Living with the condition	
6. What is your experience of living with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection? If you are a carer (for someone with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection) please share your experience of caring for them.	

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for EGFR mutation-positive non-small-cell lung cancer 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?	
8. If there are disadvantages for patients of **current NHS treatments** for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (for example how osimertinib is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of osimertinib over current treatments on the NHS please describe these. For example, the impact 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/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
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 affects you have heard about, please describe them and explain why.	

Patient population	
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	
Equality	
12. Are there any potential equality issues that should be taken into account when considering EGFR mutation-positive non-small-cell lung cancer after complete tumour resection and osimertinib? 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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
14. Are there any important issues relevant to patients or	

carers that have been missed in ERG report?	

PART 3 -Key messages

15. In up to 5 sentences, please summarise the key messages of your statement:

-
-
-
-
-

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.

……

Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Thursday 20 May 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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. The text boxes will expand as you type.

Important information on completing this expert statement

- 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 want 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 15 pages.

PART 1 – Living with or caring for a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection and current treatment options	
About you	
1.Your name	**Angela Terry**
2. Are you (please tick all that apply):	☒ a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	EGFR Positive UK
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where 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/experience (e.g. 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
Living with the condition	
6. What is your experience of living with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection? If you are a carer (for someone with EGFR mutation-positive non-small-cell lung cancer after complete tumour resection) please share your experience of caring for them.	In Feb 2019, following a skiing accident and an x-ray in A&E (Austria), a suspicious shadow on my right lung led to a lung cancer diagnosis and a subsequent right uniportal VATS lower lobectomy (Vienna). Histology identified EGFR positive NSCLC. I was 65yrs old, asymptomatic, fit and active and a never smoker. A PET scan in March 2019 (Oxford) identified a L4 metastasis. It took me about 1 month to fully recover from the resection however this was a very stressful time as the clinical team in Oxford could not agree on a treatment plan to deal with the newly identified L4 lesion. My Oncologist favoured a surgical intervention however this was denied by the MDT, then radical radiotherapy which was also denied as it was not available at that hospital. I was left with the proposal of Afatinib. At this point I secured a second opinion and am now under the care of The Royal Marsden. My treatment plan began immediately and I started taking Afatinib in May 2019 and the L4 lesion was treated by CyberKnife SBRT in June 2019.

	My confidence levels grew knowing that the 2 identified sites of 'hot' cancer activity had been removed or zapped and that for the moment Afatinib was dealing with any circulating disease. Two years into treatment I have developed a regime and techniques to deal with the numerous but not constant side effects of my TKI. I have 3 monthly CT scans and Zometa infusions and 6 monthly MRI scans. All of my scans have shown 'stable disease' and I am once again very fit and active. The convenience of a daily TKI tablet means my disease has minimal impact on the pattern of my life. I neither feel nor look ill.
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for EGFR mutation-positive non-small-cell lung cancer 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?	7a 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 beyond a certain amount of time from the operation its impact lessens. I was left with the distinct impression that the chemo was not altogether necessary and had the L4 lesion not been identified I would probably not have taken up the option of Chemo. Once the L4 lesion was identified the situation of course changed. Complete resection is psychologically powerful as it removes the currently active cancer. Anything that then suggests a possible cure is to be grabbed but not if it is only partially effective. 7b 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. Compare this to a highly rated daily tablet taken in your own home - no comparison.
8. If there are disadvantages for patients of **current NHS treatments** for EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (for example how osimertinib is given or	The side effects of Osimertinib as described by others are much less than the older generation TKI's and certainly less than Chemo. The huge advantage must be less time in hospital being 'done to' i.e. the clinical staff administering the treatment at a time and in a way that fits with their workload and schedule. I regularly wait for up to 60 – 75mins for my Zometa infusion to

taken, side effects of treatment etc) please describe these	begin. even though the actual infusion takes only 20 mins to administer. The staff are wonderful but the logistics don't always work out in line with the patient appointment time. Knowing that there is another treatment that is more effective than the one you are on is very upsetting. The sense of unfairness and one's inability to influence the situation is draining.
Advantages of this treatment	
9a. If there are advantages of osimertinib over current treatments on the NHS please describe these. For example, the impact 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/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	9a The positive impact of knowing that you are on the best drug available for your condition Daily tablet taken at home. Manageable side effects which do not restrict usual everyday activity. Confidence in the efficacy of Osimertinib as opposed to Chemo. Less time in hospital. Feeling in control of my treatment. Able to be fully engaged with my family life. Loved ones seeing how well I am doing affects their anxiety and behaviour. Increasing personal belief and confidence that with this regime I can continue to live well. 9b Knowing I am on the best drug available for my condition. Daily tablet taken at home. 9c Going to hospital makes us very aware of our illness. Taking my daily tablet at home, at a time that suits me, has a much less negative impact. I follow my side effect management regime and take my tablet, all done in under 30 mins and I can

	get on with my day like any normal person! No-one else needs to be involved in my daily treatment so it has no impact at all on my family.
Disadvantages of this treatment	
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 affects you have heard about, please describe them and explain why.	Cost 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
Patient population	
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	Hospital visits are difficult for anyone but especially those patients with mobility or cognitive issues Taking a single daily tablet is easier for anyone to incorporate into their daily routine If a patient develops brain metastasis as is very common with EGFR they will be excluded from driving so may need to involve others in getting them to appointments

Equality	
12. Are there any potential equality issues that should be taken into account when considering EGFR mutation-positive non-small-cell lung cancer after complete tumour resection and osimertinib? 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 More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	For me 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.

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
14. Are there any important issues relevant to patients or carers that have been missed in ERG report?	None that I am aware of.
PART 3 -Key messages	
15. In up to 5 sentences, please summarise the key messages of your statement: Taking a daily TKI has minimal impact on me or my family and enables this patient to live a full and active life.	

Continued use of Osimertinib after 3 years is not recommended. Why 3 years and if the patient is doing well what would be the recommended replacement treatment?

What treatments are offered in the adjuvant setting of other Cancer groups? Is it only Chemo? Lung Cancer does not always receive the same attention as other cancers, might the proposed restricted use of Osimertinib be another example of that.

Under the current proposal, if Osimertinib is prescribed in the adjuvant setting it may not be available as a later treatment / re-challenge. This would mean some patients lose out on a potentially beneficial later treatment.

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. Compare this to a highly rated daily tablet taken in your own home - there is no comparison.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Thursday 20 May 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.

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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	[redacted] For Royal College of Pathologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No Disclosures**

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS	NO	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 2: Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib	**no**	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 3: Uncertainty surrounding company's cure assumptions and OS predictions	**YES**	Agree with ERG report regarding uncertainties as the medium timeframe is short and uncertain whether adjuvant osimertinib will prevent, or only delay, disease recurrence beyond this timepoint.
Key issue 4: Uncertainty regarding re-treatment with osimertinib	**n**o	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 5: Limitations of available utility values for EGFRm-positive NSCLC	no	Please provide your response to this key issue, including any new evidence, data or analyses
Key issue 6: Absence of subgroup analyses for patients with stage IB NSCLC	**y**es	"If the evidence allows, subgroups based on NSCLC stage (IB versus II-IIIA) may be considered ". Cost implication on diagnostic pathway needs to be considered

		EGFR mutations are seen in smokers too – so cannot discriminate smokers against non smokers. • In the absence of reflex testing, if the ten weeks stands, and there are no other constraints, in an ideal situation, this is sufficient to report the resection specimen and then obtain the EGFR mutation status on resected material, provided the request is made at a timely manner and conveyed to the pathologist. • (work force shortages will be the main bottle neck If lung cancer screening in UK is widened across centres- then the cohort of stage 1b cancers and stage 2 cancers will increase as there will be 150 cancers for every 3000 patients screened.)

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: I If the evidence allows, subgroups based on NSCLC stage (IB versus II-IIIA) may be considered nsert additional issue	Expansion of Issue 6 of the ERG report that discusse**s** this issue	**yes**	Cost implications will need to be considered in the diagnostic pathway if lung cancer screening is adopted as more patients identified through screening will be in this cohort . • If the pathway proceeds to test for EGFR at early stages for neoadjuvant IO then the mutation status will be important to establish from the diagnostic biopsy . Reflex testing of diagnostic biopsies will have an added cost pressure on the pathway as all early adenocarcinomas with PS1/PS2 will need to be tested to maintain no one is discriminated . At present reflex EGFR testing is mainly advocated for Stage3 and 4 cancers.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	**Company's base case before technical engagement**	**Change(s) made in response to technical engagement**	**Impact on the company's base-case ICER**
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

NICE National Institute for Health and Care Excellence

Technical engagement response form

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection [ID3835]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
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About you

Your name	[redacted], RCP registrar
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Uncertainty surrounding whether a benefit in DFS will translate to a benefit in OS		The OS outcome data remains immature, and as such, uncertainty remains around the extent to which adjuvant osimertinib prevents disease recurrence verus delays disease recurrence.
Key issue 2: Uncertainty surrounding downstream treatment pathways with or without adjuvant osimertinib		Our experts agree with the assumptions made regarding treatment beyond adjuvant osimertinib. Patients with loco-regional recurrence would be offered surgery or radiotherapy where possible. Patients that develop distant recurrence during adjuvant treatment are likely to be offered platinum-doublet chemotherapy (PDC). Patients that develop distant recurrence following completion of adjuvant treatment would be offered further TKI therapy (currently osimertinib in preference to other TKIs); following progression on TKIs, patients may be offered PDC. The proportion of patients that would be offered quadruple therapy (PDC + atezo + bev) is small.
Key issue 3: Uncertainty surrounding company's cure assumptions and OS predictions		Current treatment pathways for early stage disease involve a relatively short active treatment phase. A 5 yr timepoint as a surrogate marker for cure is applicable in this context. However, 5 yrs from diagnosis may be less relevant as a timepoint for measuring cure in the proposed pathway that includes 3 yrs of active treatment.

Key issue 4: Uncertainty regarding re-treatment with osimertinib		See above
Key issue 5: Limitations of available utility values for EGFRm-positive NSCLC		
Key issue 6: Absence of subgroup analyses for patients with stage IB NSCLC		Within the subgroup analyses included, improvement in DFS appears to extend to stage Ib patients, and thus appropriate to include within these patients within a final recommendation.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection: A Single Technology Appraisal

Addendum: ERG's commentary on the company's technical engagement response

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1. Introduction

This addendum relates to the Single Technology Appraisal (STA) of osimertinib for adjuvant treatment of epidermal growth factor receptor mutation-positive (EGFRm-positive) non-small-cell lung cancer (NSCLC) after complete tumour resection. Following the submission of the Evidence Review Group (ERG) report,[1] responses to technical engagement were provided by the company (AstraZeneca), as well as by the Royal College of Pathologists, three clinical experts and two patient experts. The company's technical engagement response[2] includes the following additional data and analyses:

- [redacted]
- [redacted]
- An updated set of cost-effectiveness results which replace the ERG's timepoint for cure in the adjuvant osimertinib group in the pessimistic scenario from 8 years to 6 years (see company's technical engagement response,[2] Appendix A). These analyses also exclude two of the ERG's additional sensitivity analyses (ASA4b and ASA5).

Section 2 of this ERG addendum presents a brief commentary on the company's technical engagement response.[2] Section 3 summarises the ERG's view regarding the company's additional economic analyses. The ERG has not undertaken further exploratory analyses as part of this addendum.

2. ERG commentary on company's technical engagement response

Table 1 summarises the key points raised in the company's technical engagement response together with a brief commentary from the ERG.

Table 1: Summary of company's technical engagement response and ERG commentary

Issue	Summary of company's technical engagement response	ERG commentary on company's response
Key issue 1: Uncertainty surrounding whether a benefit in disease-free survival (DFS) will translate to a benefit in overall survival (OS)	• The company's technical engagement response[2] states that DFS is a clinically relevant and accepted endpoint in resected EGFRm-positive NSCLC. • There is significant intrinsic value in extending DFS in patients with resected EGFRm NSCLC. • The company's response [redacted] • The company's response provides [redacted] • The company's response states that adjuvant osimertinib is expected to result in a significant OS benefit, as stated by clinicians interviewed by the company This expectation is based on: (i) the magnitude of DFS benefit in ADAURA,[5] which is greater than that observed in earlier generation EGFR-tyrosine kinase inhibitor (TKI) trials in the adjuvant setting; (ii) the reduced rate of recurrence with distant or central nervous system (CNS) metastases with osimertinib versus placebo; (iii) the benefits in OS and CNS recurrence with osimertinib versus first- and second-generation EGFR-TKIs in the metastatic NSCLC setting.	The ERG agrees that DFS is a clinically relevant endpoint and that there is value in extending DFS in patients with resected EGFRm NSCLC. The burden of disease from EGFRm NSCLC is summarised in Section 2.1.3 of the ERG report.[1] DFS results from the ADAURA trial of osimertinib are presented in Section 4.2.3 of the ERG report. The available data on OS from ADAURA and its limitations are described in Section 4.2.3 of the ERG report.[1] [redacted] The ERG agrees that the reasons provided as to why adjuvant osimertinib is expected to result in a significant OS benefit are all plausible. However, due to the immaturity of OS data from ADAURA[5] (9 deaths [2.7%] in the osimertinib arm and 20 deaths [5.8%] in the placebo arm), the magnitude of any OS benefit is very uncertain. The impact of this uncertainty has been explored within the ERG's exploratory analyses (see ERG report, Section 5.4). The company's technical engagement response does not present any additional evidence which addresses this uncertainty.
Key issue 2: Uncertainty surrounding	• The company's technical engagement response[2] states that osimertinib (rather than earlier generation EGFR-TKIs) is the current standard of care for first-line locally advanced and metastatic EGFRm NSCLC.	The ERG's preferred analyses assume that of those patients in the active monitoring group who develop distant metastases, all will receive first-line treatment with

Issue	Summary of company's technical engagement response	ERG commentary on company's response
downstream treatment pathways with or without adjuvant osimertinib		osimertinib. This is consistent with the company's base case analysis.[6] National prescribing data provided by the company in response to the factual accuracy check of the ERG report indicate that around [redacted] of patients receive osimertinib in the first-line metastatic setting, and that a proportion of patients instead receive other TKIs (afatinib, erlotinib, gefitinib or dacomitinib).[7] The ERG report[1] includes an additional sensitivity analysis ("ASA3") which assumes that a mix of TKIs is used, based on the prescribing data provided by the company (see ERG report, Table 49). Whilst this sensitivity analysis highlights that the ICER for adjuvant osimertinib is expected to be higher if other TKIs are included as treatments in the metastatic setting, the ERG's clinical advisors believe the use of osimertinib as a first-line treatment for metastatic disease will increase in the future. However, this may not be the case if adjuvant osimertinib were to receive a positive NICE recommendation and if re-treatment with a TKI is not permitted.
Key issue 3: Uncertainty surrounding company's cure assumptions and OS predictions	• The company's technical engagement response[2] states that clinical trial evidence in resected NSCLC demonstrated a plateauing effect in DFS rates at approximately 48-60 months following surgical resection, indicating that 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. This is based on trial evidence presented in Section B.3.3.3.1 of the CS.[6] • [redacted] • The company believes that the ERG's preferred pessimistic analysis is	The ERG's views regarding the company's cure assumptions and resulting OS predictions are described in Section 5.3.4 of the ERG report (critical appraisal point 4).[1] The ERG's views remain unchanged – there is uncertainty surrounding the company's cure assumptions and the magnitude of additional OS benefit for adjuvant osimertinib versus active monitoring. The company's technical engagement response[2] does not provide any additional data which can reduce this uncertainty. [redacted]

Issue	Summary of company's technical engagement response	ERG commentary on company's response
	excessively pessimistic. This analysis assumes cure at 5 years in the placebo arm, and at 8 years in the osimertinib arm (i.e. 5 years plus the 3-year maximum adjuvant osimertinib treatment time). • The company's response presents updated economic analyses which move the cure timepoint for adjuvant osimertinib in the ERG's pessimistic scenario from 8 years to 6 years (3-year maximum treatment time plus 2 years to account for delayed disease recurrence, with an extra year added to remain conservative). • The company's response states that the ERG's additional sensitivity analysis 5 (ASA5) is clinically implausible and contradicts clinical data and opinion.	[redacted] The ERG does not believe that the company's updated economic analyses fully represent the uncertainty surrounding the available OS data from ADAURA[5] or the extent to which adjuvant osimertinib will lead to cure and extended OS. The ERG does not consider the company's amended pessimistic scenario to be conservative. This issue is discussed further in Section 3 of this addendum. As discussed in the ERG's response to Key Issue 1, there remains uncertainty around the extent to which the DFS benefit will be maintained and translated into OS benefit. The ERG's clinical experts highlighted a potential situation whereby osimertinib delays some relapses rather than preventing them altogether. This concern is also briefly highlighted in the response from the Royal College of Pathologists. In light of this uncertainty, the ERG report[1] presents a range of scenarios which explore this uncertainty. Of these analyses, ASA5 is the most pessimistic. The ERG believes that this analysis is a potentially helpful marker for the Appraisal Committee, as it represents fully the assumption that disease relapse is delayed by osimertinib rather than avoided and can thus be interpreted as a worst-case scenario.
Key issue 4: Uncertainty regarding re-treatment with osimertinib	• The company's technical engagement response[2] states that re-treatment with osimertinib in the metastatic setting is supported by UK clinical opinion.	The ERG believes that this issue is a matter for NHSE to address. Whilst the ERG's preferred analyses assume that re-treatment is not permitted, Table 49 of the ERG report[1] includes an additional sensitivity analysis (ASA7) in which re-treatment is permitted. This analysis indicates that including re-treatment has a limited effect on the ICER for adjuvant osimertinib; this is because the probability of relapse after the 5-year timepoint for re-treatment is

Issue	Summary of company's technical engagement response	ERG commentary on company's response
		assumed to be low.
Key issue 5: Limitations of available utility values for EGFRm-positive NSCLC	• The company response agrees with the ERG report that there is a significant lack of published utility values for resected EGFRm NSCLC.	The ERG's concerns regarding the utility values applied in the model can be found in Section 5.3.4 of the ERG report (critical appraisal point 10).[1] The ERG's exploratory analyses include an additional sensitivity analysis in which alternative utility values from Andreas *et al.*[8] are applied; the impact on the ICER is limited. The ERG has no further comments on this issue.
Key issue 6: Absence of subgroup analyses for patients with stage IB NSCLC	• The company response[2] states that there is an unmet need in stage IB disease for effective, targeted adjuvant treatments. • The company response states that osimertinib has demonstrated a significant DFS benefit in stage IB, based on ADAURA.[5] • The company response states that adjuvant osimertinib for stage IB will be a cost-effective use of NHS resources. They state that cost-effectiveness has not been assessed in stage IB patients since effectiveness data are immature in this subgroup, but that the company's ICERs are £9,979 per quality-adjusted life year (QALY) gained for the overall population (stage IB-IIIA) and £5,292 per QALY gained for the stage II-IIIA subgroup. They state that we can therefore expect that treatment of stage IB will represent a cost-effective use of NHS resources. • The company believes that it is inappropriate to consider an analysis by subgroup and cites the recent appeal in NICE Technology Appraisal 504 (pirfenidone for treating idiopathic pulmonary fibrosis).	The ERG agrees that there is an unmet need in patients with stage IB disease and that the subgroup analyses from ADAURA[5] indicate that osimertinib is effective in this patient subgroup. However, the ERG's concerns regarding the cost-effectiveness of adjuvant osimertinib in this population remain unchanged (see ERG report,[1] Section 5.3.4, critical appraisal point 13). The company's technical engagement response[2] does not include an economic subgroup analyses for the stage IB population. The company's subgroup analyses for the stage II-IIIA population indicate that the ICER is lower than that for the overall population; this indicates that the ICER for osimertinib will be higher in the stage IB subgroup compared with the ICER for the overall population. With respect to the company's more general argument that it is inappropriate to consider subgroup analyses, the ERG disagrees for several reasons: • The stage IB subgroup is identifiable • The inclusion of subgroup analyses by stage (stage IB versus II-IIIA) was listed in the "Other considerations" section of the final NICE scope[9] • On the basis of the ICERs for the overall population and the stage II-IIIA subgroup presented by the company,[6, 10] there is uncertainty regarding whether adjuvant osimertinib might represent a good use of

Issue	Summary of company's technical engagement response	ERG commentary on company's response
		NHS resources in the stage IB subgroup. The ERG acknowledges that the available data for the stage IB subgroup in ADAURA[5] are subject to small numbers of events which, in turn, will lead to considerable uncertainty around the estimated ICER. However, in the absence of this analysis, the cost-effectiveness of osimertinib for this subgroup remains unknown.

3. ERG commentary on company's additional economic analyses

Appendix A of the company's technical engagement response[2] includes the results of an updated set of cost-effectiveness results, based on optimistic and pessimistic assumptions regarding the cure timepoint for adjuvant osimertinib. There are two key differences between the company's updated economic analyses and the exploratory analyses presented in the ERG report:[1]

(i) The company's pessimistic scenario moves the timepoint for cure in the adjuvant osimertinib group from 8 years to 6 years;

(ii) The company's updated analyses purposefully exclude two of the ERG's additional sensitivity analyses which applied alternative survival distributions for recurrence in the adjuvant osimertinib group on the basis that they are *"not clinically plausible"* (ASA4b and ASA5). These additional sensitivity analyses reflect pessimistic assumptions regarding the benefits of adjuvant osimertinib and generated ICERs which were markedly higher than the ERG's preferred scenarios.

It should be noted that Figure 23 of the original ERG report[1] already provided a sensitivity analysis which assumed a 6-year cure timepoint for adjuvant osimertinib alongside the ERG's other preferred assumptions; hence, the company's preferred pessimistic scenario is not new. In addition, the ERG does not agree that it is appropriate to exclude ASA4b or ASA5 as these analyses provide potentially useful information regarding the maximum bound of the ICER under particularly pessimistic assumptions. Overall, the ERG believes that the limited range between the cure timepoints applied in the company's preferred optimistic and pessimistic scenarios and the exclusion of ASA4b and ASA5 fails to fully reflect the uncertainty in the available evidence for adjuvant osimertinib. The ERG considers that the exploratory analyses presented in the original ERG report provide a more balanced consideration of the uncertainty surrounding the cost-effectiveness of adjuvant osimertinib.

4. References

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